



Linking biological pathways, networks and disease

Robin Haw
19th August 2014
COMBINE 2014 Meeting



International
Cancer Genome
Consortium



Ministry of Research and
Innovation



National Human
Genome Research
Institute

www.reactome.org



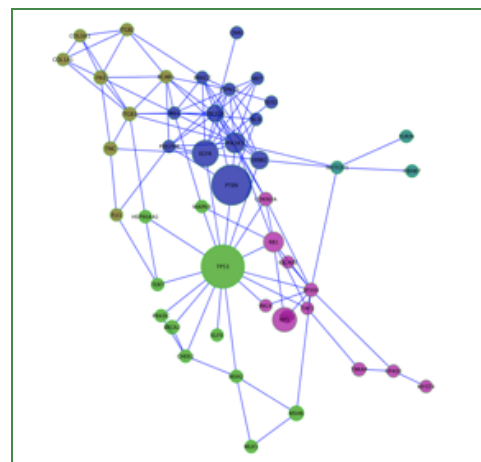
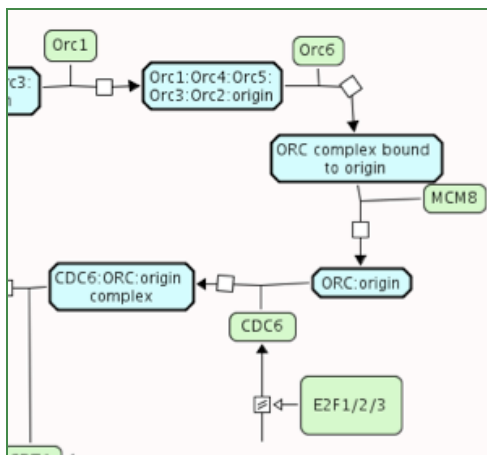
Overview

- Content
 - Controlled Vocabularies
 - Disease Pathway Curation
- Visualization and Analysis
 - New Pathway Browser
- Exchange
 - SBML, SBGN, BioPAX, PSIQUIC

What is Reactome?



- Open source and open access pathway database
- 1500+ pathway modules encompassing many areas of human biology.
 - V49 has annotations for 7684 human proteins, 7332 reactions, and 1462 small molecules, based on data from 16900 literature references.
- Provides tools and datasets for browsing and visualizing pathway data.



www.reactome.org

Controlled vocabularies for entities and events

- Created unique, unambiguous names for pathway events and molecular entities.
- Significantly improves consistency and readability of names.
- Benefits for searching and data mining within and between databases.
- Reduced curation burden.

Peptide CV Names

- Gene Symbol Core - HGNC approved gene symbols
- Peptide coordinates suffix
 - Refers to UniProt ‘Chain’ Feature
 - e.g. large and small subunits of CASP9 - **CASP9(1-315)** and **CASP9(316-416)**
- Post-translational modification (PTM) prefixes
 - Abbreviated from PSI-MOD
 - Includes coordinate of PTM (if known)
- Phosphorylation subtypes grouped as one class, ordered by coordinate.
 - DAPPI phosphorylated on tyrosine-139 = **p-Y139-DAPPI**
 - WASF2 phosphorylated on tyrosine-150, serine-343 and threonine-346 = **p-Y150,S343,T346-WASF2**
 - GAB2 tyrosine-phosphorylated at unknown coordinate = **p-Y-GAB2**
 - GLI3 phosphorylated, unknown residue = **p-GLI3**

Complex and set CV names

- Concatenated string of component or set member names.
- Comma separator for sets, colon for complexes.
 - G protein-activated inward rectifier potassium channels = **KCNJ3,KCNJ5,KCNJ6,KCNJ9**
 - Complex of IL3, IL3RA, IL3RB, and JAK2 = **IL3:IL3RA:IL3RB:JAK2**
- Entity occurs more than once, name is preceded by *nx*
 - Complex of 2 molecules of PPOX and one of FAD = **2xPPOX:FAD**
 - *n*mer names e.g. dimer, hexamer allowed for homomers
- ‘Candidates’ (possible members) named in round brackets
 - Set of HRH2, HRH3, plus possible ‘candidate’ members HRH6 and HRH8 = **HRH2,HRH3,(HRH6,HRH8)**
- Precedence or hierarchical structure indicated with square brackets
 - Complex ABC1:ABC2 binds complex ABC3:ABC4 = **[ABC1:ABC2]:[ABC3:ABC4]**

Small molecule (chemical) CV names

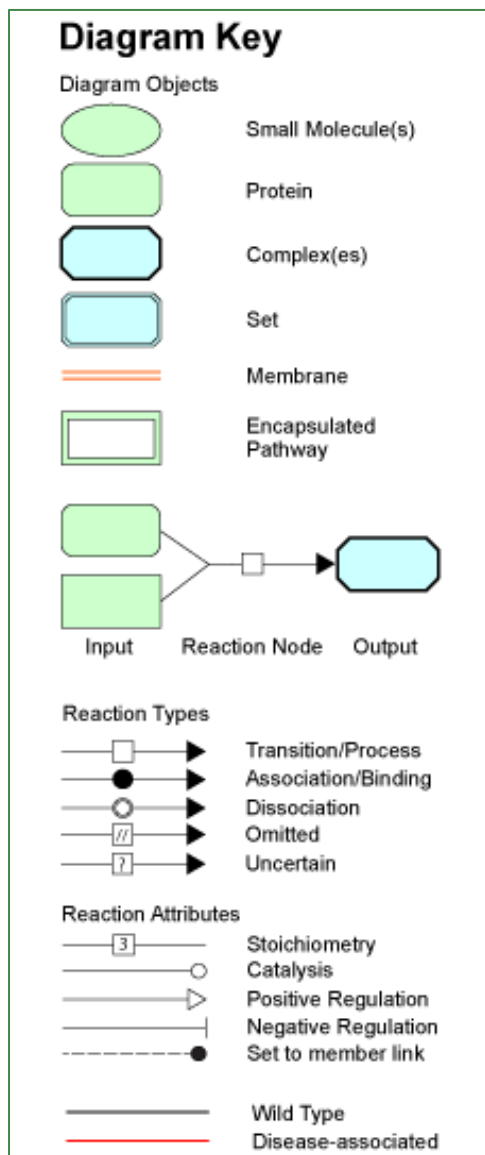
- Standardised abbreviation for >1400 small molecules in Reactome
- Sourced from ChEBI, KEGG Compounds, PubChem, or literature
- Checked for precedence/ambiguity at <http://www.allacronyms.com>
- e.g. Calcium ion = **Ca2+**
- adenosine triphosphate = **ATP**
- Diacylglycerol = **DAG**
- 4-(4-(dimethylamino)styryl)-N-methylpyridinium = **4-Di-2-ASP**
- D-Glyceraldehyde 3-phosphate = **GA3P**

Pathway event (reaction) CV names

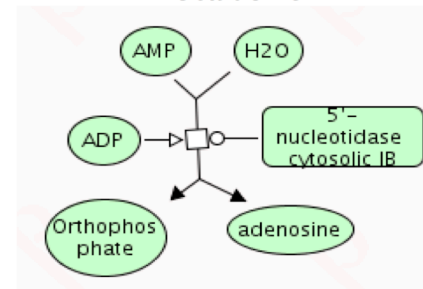
- A small set of CV terms - can be applied automatically using simple rules:
 - Transformation (default) a (,b and c) **TRANSFORMS TO** d (,e and f)
 - Binding, Dissociation a BINDS b forming c, c **DISSOCIATES TO** a **AND** b
 - Polymerization a (,b and c) **POLYMERIZE TO** x
 - Transfer reactions a **TRANSFERS** b **TO** c1 (**TO FORM** c2)
 - Passive transport a **TRANSLOCATES FROM** [x] **TO** [y]
 - Active transport a **TRANSPORTS** b (**FROM** x **TO** y)
 - Antiporter a **EXCHANGES** b **FOR** c (across x membrane)
 - Cotransporter a **COTRANSPORTS** b (,c) **WITH** d (,e)
 - Activation (conformational) a (,b) **IS (ARE) ACTIVATED**
 - Catalysis* (default) a **CATALYZES** b (,c and d) **TO** e (,f and g)

*Catalyst with defined GO molecular function

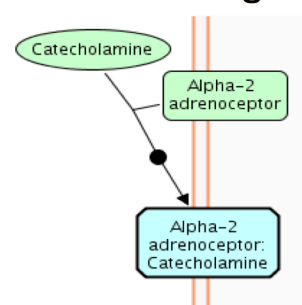
Reactome supports minimal SBGN PD glyphs



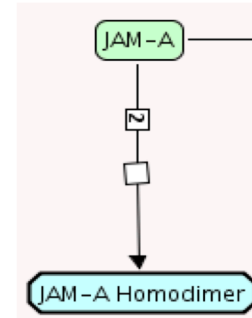
Metabolic



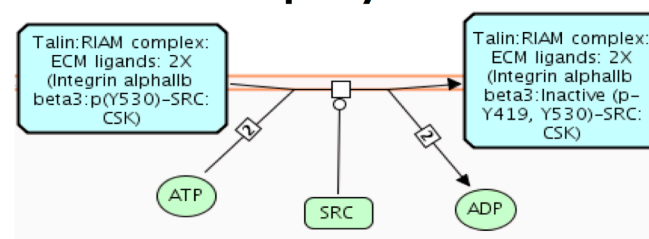
Binding



Dimerization

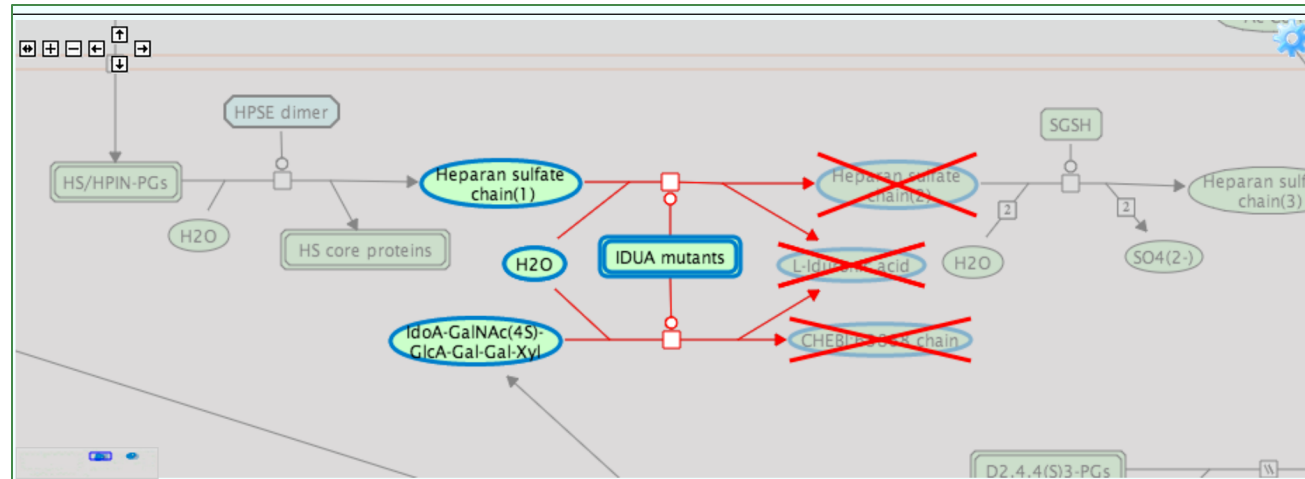


Phosphorylation

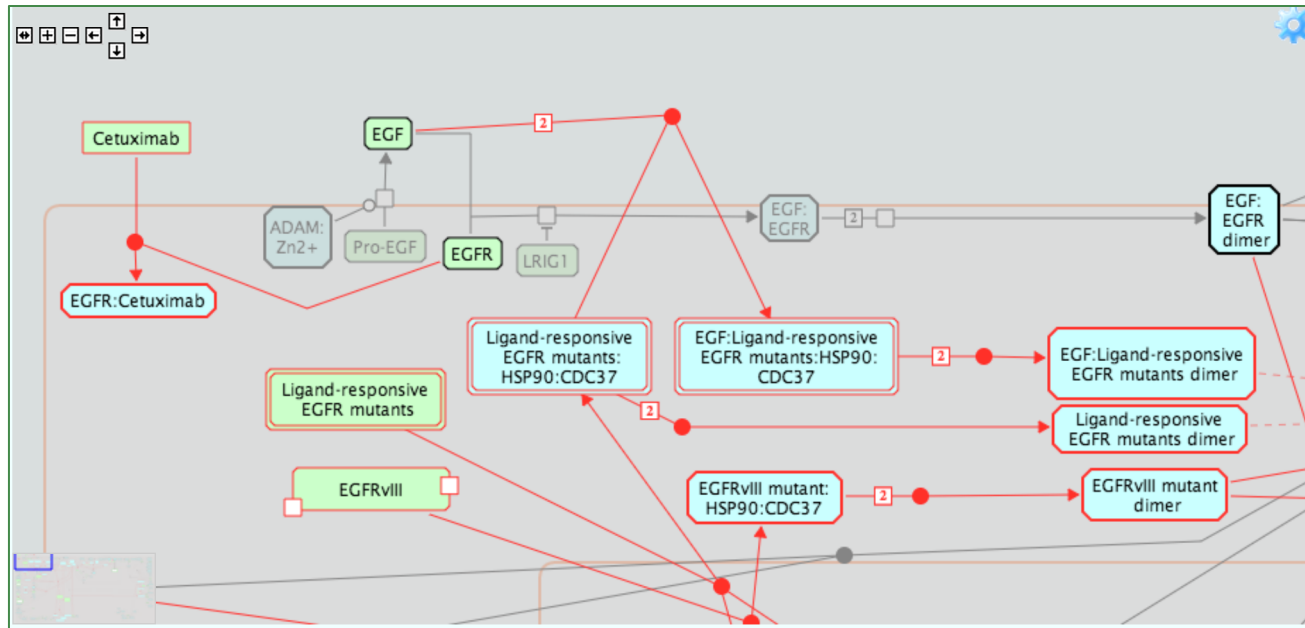


Disease Pathway Curation

Monofactorial genetic disease



Polygenic disease



SBGN Pathway Browser

- Google-map style pathway diagrams

REACTOME

Pathways for: Homo sapiens

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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

Balanced reactions from Rhea

REACTOME

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Protein ☐ Small molecule ☒ Complex ☐

Overview | **Molecules (6)** | Structures (1/1) | Expression | Processes | Downloads

RHEA:16846

acetyl-CoA	+	H2O	+	oxaloacetate	=>	citrate
CHEBI:57288	+	CHEBI:15377	+	CHEBI:16452	=>	CHEBI:16947

Protein structures from PDBe

REACTOME

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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

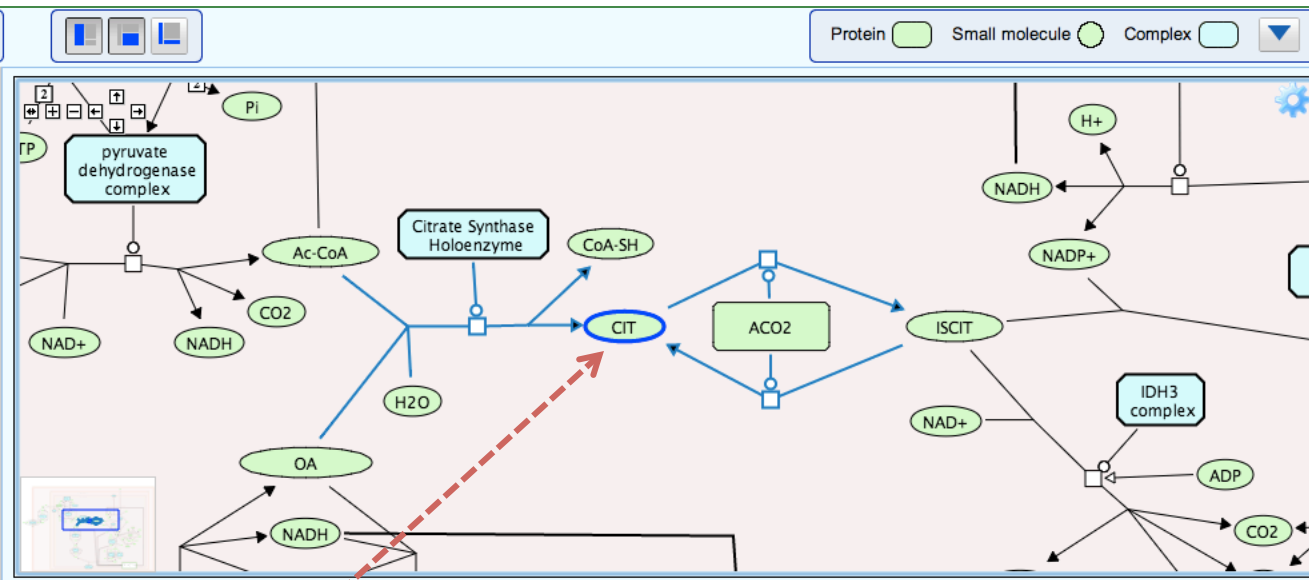
Chemical structures from ChEBI

REACTOME

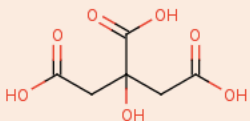
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Overview | Molecules | Structures (1/1) | Expression | Processes | Downloads



ChEBI Name	citric acid
ChEBI ID	CHEBI:30769
Definition	A tricarboxylic acid that is propane-1,2,3-tricarboxylic acid bearing a hydroxy substituent at position 2.
Stars	★★★★
Secondary ChEBI IDs	CHEBI:3727, CHEBI:340769, CHEBI:41523, CHEBI:23322

Expression data from the Expression Atlas

REACTOME Pathways for: **Homo sapiens**

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Diagram: The diagram illustrates the Citric Acid Cycle (TCA cycle) and its connection to pyruvate metabolism. 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 component involved in the conversion of CIT to isocitrate (ISCIT).
- IDH3 complex**: Converts ISCIT to alpha-ketoglutarate, releasing CO2 and NADH.
- Regulation**: The diagram shows various regulatory points, including the inhibition of the pyruvate dehydrogenase complex by NADH and the regulation of Citrate Synthase by NADH and CoA-SH.

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																

PSICQUIC - Interaction Data from STRING

REACTOME

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Protein ☒ Small molecule ☒ Complex ☐

Overview | Molecules | Structures | Expression | Processes | Downloads

ACO2 [mitochondrial matrix] Species: **Homo sapiens**

Involved in pathways

- Citric acid cycle (TCA cycle) [Homo sapiens]

Other forms of this molecule

- ACO2(1-780) [cytosol]
- ACO2(1-780) [mitochondrial intermembrane space]

Pathway Diagrams support Reactome Tools

- Pathway Mapping and Enrichment Analysis
- Expression Overlay onto Pathways
- Compare Pathways between Species

In 2 months reached 6,622 analysis
(15/09/14)

BETA REACTOME

Pathways for: Homo sapiens

Tour this pathway browser? [Hide](#)

Protein ☐ Small molecule ☐ Complex ☐

Event Hierarchy:

- Disease (27/1,515) FDR: 9.95E-1
 - HIV Infection (1/240) FDR: 9.99E-1
 - Influenza Infection
 - Latent infection of Homo sapiens with Mycobacterium tuber
 - Signaling by EGFR in Cancer (10/213) FDR: 3.23E-1
 - Amyloids (1/58) FDR: 7.91E-1
 - Neurotoxicity of clostridium toxins
 - Signaling by FGFR in disease (14/212) FDR: 2.46E-1
 - Signaling by FGFR (10/181) FDR: 2.46E-1
 - Signaling by FGFR mutants (8/70) FDR: 2.46E-1
 - Abnormal metabolism in phenylketonuria
 - Mucopolysaccharidoses (1/181) FDR: 9.93E-1
 - Diseases associated with visual transduction (1/152) FDR
 - PI3K/AKT Signaling in Cancer (5/129) FDR: 4.17E-1
 - Signaling by NOTCH1 in Cancer (1/82) FDR: 8.91E-1
 - Abnormal conversion of 2-oxoglutarate to 2-hydroxyglutarate
 - Glycogen storage diseases (8/380) FDR: 8.06E-1
 - Defects in vitamin and cofactor metabolism (3/180) FDR: 8
 - Signaling by TGF-beta Receptor Complex in Cancer

DNA Repair

- DNA Replication (2/116) FDR: 8.21E-1
- Extracellular matrix organization (10/291) FDR: 4.17E-1
- Collagen formation (1/99) FDR: 9.31E-1
- Fibronectin matrix formation
- FN1 binds Collagen types I-V, VII
- Elastic fibre formation
- Laminin interactions (5/34) FDR: 2.46E-1

Signaling by FGFR mutants (8/70) FDR: 2.46E-1

1/5, 10h, control

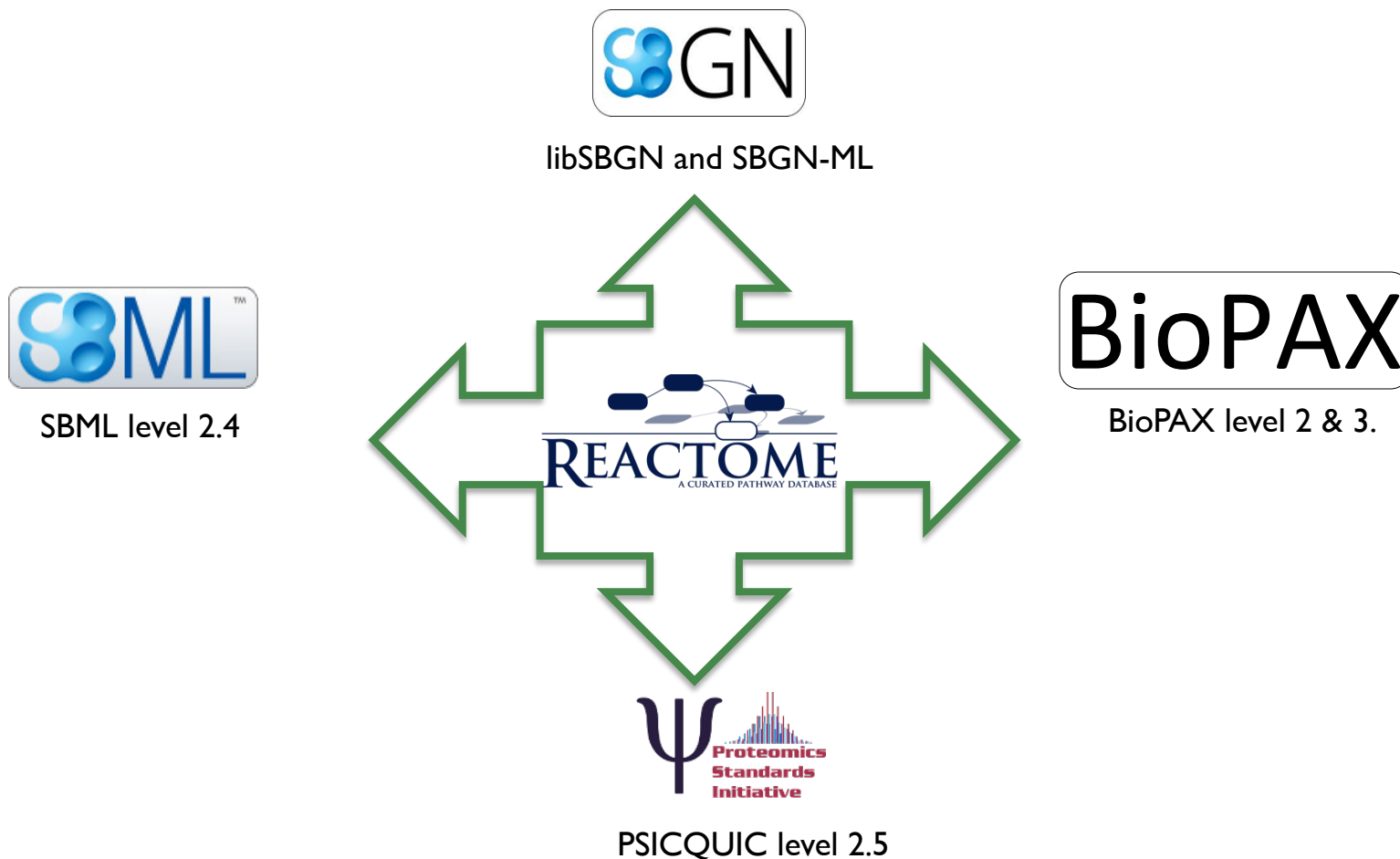
Overview Molecules Structures Expression Analysis (575) Processes Downloads

Results for: TOTAL (575) Type: Overrepresentation [Data: Gene_names_from_liver]

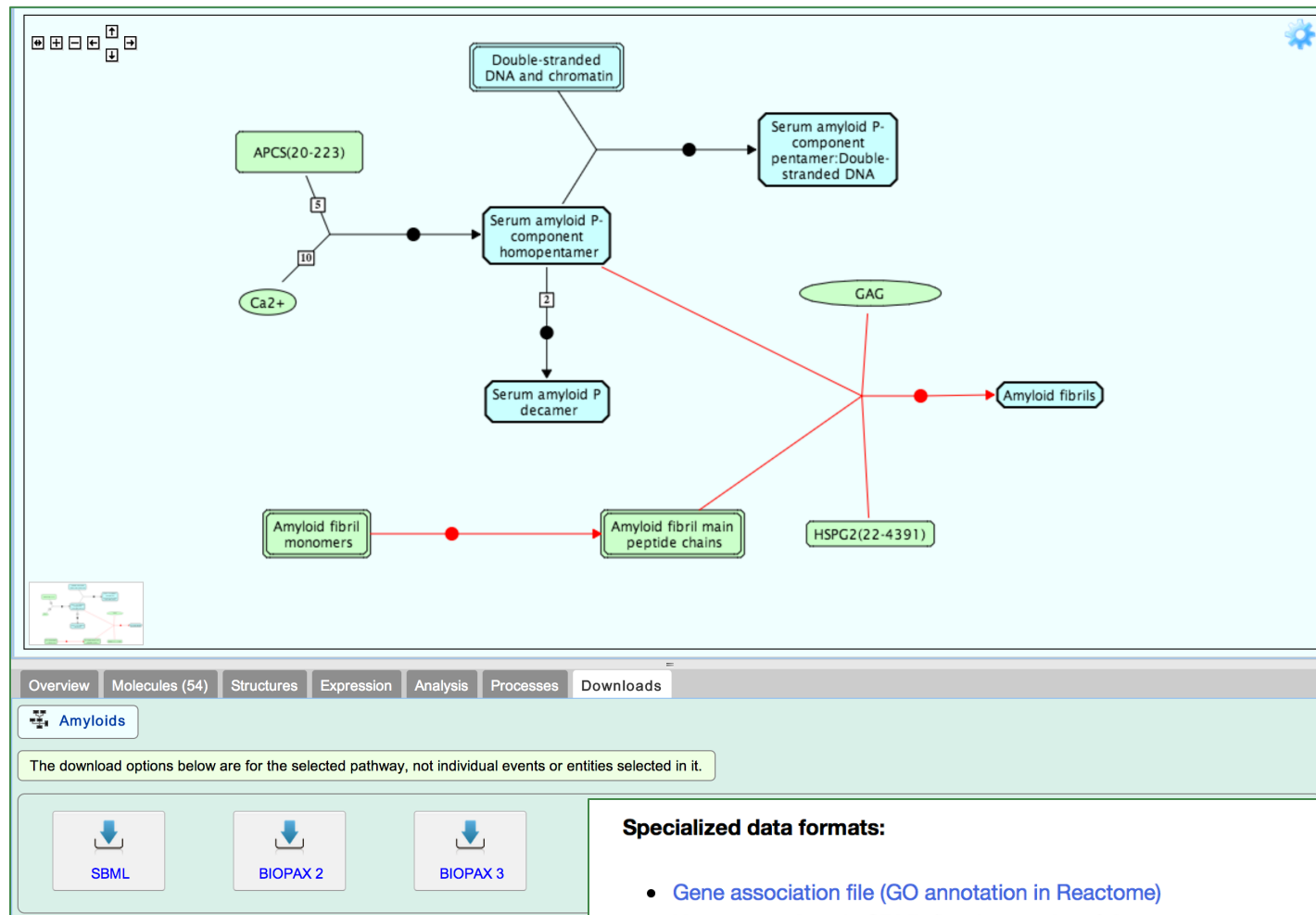
Pathway name	Entities found	Entities Total	Entities ratio	Entities pValue	Entities FDR	Reactions found	Reactions total	Reactions ratio
Signaling by FGFR mutants	8	70	0.008	7.06E-4	2.46E-1	40	62	0.009
Signal regulatory protein (SIRP) family interactions	4	18	0.002	1.54E-3	2.46E-1	10	10	0.001
Laminin interactions	5	31	0.003	1.65E-3	2.46E-1	12	15	0.002
Signaling by FGFR in disease	14	212	0.023	2.05E-3	2.46E-1	87	181	0.026
SHC-mediated cascade	5	39	0.004	4.38E-3	2.46E-1	4	4	0.001
EGFR Transactivation by Gastrin	3	12	0.001	4.38E-3	2.46E-1	3	6	0.001

1-20 of 575

Reactome supports Open Data Standards



Single vs Bulk Pathway Downloads



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="metaid_0">
    <notes><p xmlns="http://www.w3.org/1999/xhtml">Amyloid is a term used to describe typically extracellular deposits of aggregated
    proteins, sometimes known as plaques. Abnormal accumulation of amyloid is amyloidosis, a term associated with diseased organs
    and tissues, particularly neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntingdon's. Amyloid deposits consist
    predominantly of amyloid fibrils, rigid, nonbranching structures that form ordered assemblies, characteristically with a cross
    betasheet structure where the sheets run parallel to the direction of the fibril (Sawaya et al. 2007). Often the fibril has a
    lefthanded twist (Nelson Eisenberg 2006). At least 27 human proteins form amyloid fibrils (Sipe et al. 2010). Many of these
    proteins have nonpathological functions; the trigger that leads to abnormal aggregations differs between proteins and is not
    well understood but in many cases the peptides are abnormal fragments or mutant forms arising from polymorphisms, suggesting
    that the initial event may be aggregation of misfolded or unfolded peptides. Early studies of AmyloidBeta assembly led to a
    widely accepted model that assembly was a nucleationdependent polymerization reaction (Teplow 1998) but it is now understood to
    be more complex, with multiple 'offpathway' events leading to a variety of oligomeric structures in addition to fibrils
    (Roychaudhuri et al. 2008). An increasing body of evidence suggests that these oligomeric forms are primarily responsible for
    the neurotoxic effects of Amyloidbeta (Roychaudhuri et al. 2008), alphasynuclein (Winner et al. 2011) and tau (Dance Strobel
    2009, MerazRios et al. 2010). Amyloid oligomers are believed to have a common structural motif that is independent of the
    protein involved and not present in fibrils (Kayed et al. 2003). Conformation dependent, aggregation specific antibodies suggest
    that there are 3 general classes of amyloid oligomer structures (Glabé 2009) including annular structures which may be
    responsible for the widely reported membrane permeabilization effect of amyloid oligomers. Toxicity of amyloid oligomers
    precedes the appearance of plaques in mouse models (Ferretti et al. 2011). </p><p xmlns="http://www.w3.org/1999/xhtml">Fibrils
    are often associated with other molecules, notably heparan sulfate proteoglycans and Serum Amyloid Pcomponent, which are
    universally associated and seem to stabilize fibrils, possibly by protecting them from degradation.</p></notes>
  </model>
  <annotation>
    <p xmlns="http://www.w3.org/1999/xhtml">SBML engine: Jsbnml</p><p><sbgn xmlns="http://sbgn.org/libsbgn/0.2"><map language="process
    description"><glyph class="macromolecule" id="entityVertex_7193679"><label text="APCS_20_223"/><bbox h="36.0" w="168.0"
    x="273.0" y="267.0"/><glyph class="unit of information" id="entityVertex_7193679_mt"><label text="mt:prot"/><bbox h="24.0"
    w="56.0" x="289.0" y="255.0"/></glyph><glyph class="simple chemical" id="entityVertex_7193680"><label text="Ca2"/><
    bbox h="36.0" w="90.0" x="282.0" y="282.0" y="675.0"/><glyph class="complex" id="entityVertex_7193681"><label text="Serum"/><
    bbox h="45.0" w="168.0" x="930.0" y="468.0"/><glyph class="annotation" id="entityVertex_7193681_annotation"><label text="
    APCS(20-223), Ca2+><callout target="entityVertex_7193681"><point x="1098.0" y="513.0"/><callout><bbox h="24.0" w="144.0"
    x="1114.0" y="537.0"/></glyph><glyph class="unspecified entity" id="entityVertex_7193682"><label text="
    Amyloid_fibril"/><bbox h="36.0" w="133.5" x="354.0" y="1281.0"/></glyph><glyph class="unspecified entity" id=
    "entityVertex_7193683"><label text="Amyloid_fibril_main"/><bbox h="36.0" w="181.5" x="1251.0" y="1281.0"/></glyph><glyph
    class="simple chemical" id="entityVertex_7193684"><label text="GAG"/><bbox h="36.0" w="
    glyph"><glyph class="complex" id="entityVertex_7193685"><label text="Amyloid_fibrils"/>
    y="933.0"/><glyph class="annotation" id="entityVertex_7193685_annotation"><label text="
    Serum amyloid P-component homopentamer, HSPG2(22-4391), GAG"/><callout target="entityVe
    y="969.0"/><callout><bbox h="24.0" w="760.0" x="2450.5" y="993.0"/></glyph></glyph><gl
    "entityVertex_7193686"><label text="HSPG2_22_4391"/><bbox h="36.0" w="166.5" x="1791.0"
    information" id="entityVertex_7193686_mt"><label text="mt:prot"/><bbox h="24.0" w="56.0"
    glyph"><glyph class="complex multimer" id="entityVertex_7193687"><label text="Serum"/><b
    y="930.0"/><glyph class="annotation" id="entityVertex_7193687_annotation"><label text="
    homopentamer"/><callout target="entityVertex_7193687"><point x="1099.5" y="966.0"/></ca
    x="1115.5" y="990.0"/></glyph><glyph class="unspecified entity" id="entityVerte
    "Double_stranded"/><bbox h="36.0" w="183.0" x="915.0" y="42.0"/></glyph><glyph class="c
    label text="Serum"/><bbox h="57.6" w="175.5" x="1671.0" y="219.0"/><glyph class="annota
    "entityVertex_7193689_annotation"><label text="Serum amyloid P-component homopentamer,
    callout target="entityVertex_7193689"><point x="1846.5" y="276.6"/><callout><bbox h="2
    ></glyph></glyph></glyph class="process" id="reactionVertex_7193690"><bbox h="36.0" w="3
```

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 \(800 x 600\) \(12M\)](#).
 - [XML Schema for the data model](#).
 - [WSDL file for the Reactome Web Services API](#).

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

Current and Future Work

- ORCID iD as a key mechanism for credit attribution for Reactome contributors.
- Supplement normal pathways with variant reactions representing disease states.
- Improve annotation consistency and enrich the data model.
- Work with the biocuration community for improved ontology support.
- Continued support for SBGN, SBML, BioPAX and PSI data exchange.
 - SBGN Single pathway and bulk pathways downloads.
 - Custom exports for SBML, BioPAX, SBGN via RESTful API.
- Improving the web site and resources to meet the needs of a growing and diverse user community.

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