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MouseNet v2 Tutorial (10. 05. 2015)

1. About MouseNet v2

MouseNet version 2 is an improved functional gene network for laboratory mouse, *Mus musculus*, which is the choice for many biomedical researches. To improve the previous version of [MouseNet \(Genome Biology 2008\)](#), a large volume of new microarray data derived from diverse biological contexts has been incorporated. We have also continued to improve machine learning algorithms to infer co-functional links from genomics data. MouseNet v2 now covers 88% of coding genomes with higher accuracy.

2. Network Download

Users can download whole MouseNet v2, gold standard set which are used for construction of MouseNet v2, and component networks of MouseNet v2. Furthermore we provide those networks for other eight vertebrate species (Rat, Chimpanzee, Rhesus macaque Dog, Cattle, Chicken, Western clawed frog, Zebrafish) by download options.

And, we provide coexpression networks that analyzed 8,154 of microarrays from 183 studies. Users can search contents specific coexpression networks using keywords, and download those networks for each species. Every raw data used in this study was downloaded from [Gene expression Omnibus](#).

A. Download MouseNet v2

Home

Tutorial

Network-search

Network-download

Download MouseNet V2

Download Coexpression Component Networks

Download MouseNet v2

ID type : ☒ Entrez ID ☐ Symbol

Species :

[-] MouseNet V2 : Full integrated network

| Network | Genes | Links |
|-----------------------------|--------|---------|
| MouseNet V2 | 17,714 | 788,080 |

[-] Gold Standard: Positive functional gene associations

| Set | Genes | Links |
|-----------------------------------|-------|---------|
| Gold standard set | 7,684 | 298,729 |

[-] Component networks derived directly from *Mus musculus* data

| Network | Description | Links |
|-----------------------|--|---------|
| MM-CX | Co-expression patterns of <i>Mus musculus</i> genes | 180,037 |
| MM-GN | Gene Neighborhood, Proximity between two mouse gene orthologs in Prokaryotic genomes | 157,769 |

1, 2. Choose ID type and species of interest. Networks will be downloaded according to chosen options. If a user chooses other vertebrate species except mouse, the number of genes and links could be different with mouse networks.

3. Click the hyperlink to download selected network.

B. Format of Networks.

| Gene A | Gene B | LLS |
|--------|--------|-----|
|--------|--------|-----|

*LLS = Log Likelihood Scores

Networks should be opened using Microsoft Excel or other text readers which can handle large text files.

Example of networks ->

| | | |
|---------|--------|------------------|
| S100a8 | S100a9 | 5.36055226504482 |
| Rps28 | Rpl38 | 5.32524830372245 |
| Cox6b1 | Cox7a2 | 5.29998871381872 |
| Atp5a1 | Atp5d | 5.26513597956887 |
| Rpl37a | Rpl38 | 5.25975949646318 |
| Col1a1 | Col1a2 | 5.24588820265831 |
| Rps29 | Rps28 | 5.24137610571051 |
| Ndufb9 | Ndufb8 | 5.22705678745956 |
| Atp5j2 | Uqcrl1 | 5.21096769380142 |
| Cox6b1 | Uqcrb | 5.19885233966774 |
| C1qa | C1qc | 5.19437152473506 |
| Rpl37a | Rps28 | 5.19211868933189 |
| Atp5k | Atp5j2 | 5.18500204243855 |
| Ndufb11 | Cox6b1 | 5.17641886073329 |
| Ndufb9 | Ndufc1 | 5.15856871204619 |
| Cox6b1 | Ndufb9 | 5.14195552776278 |
| Cox5a | Cyts | 5.12481470140665 |
| Rpl37a | Rplp2 | 5.12229712739531 |

C. Download coexpression component networks

Download MouseNet V2
Download Coexpression Component Networks

Download Coexpression Networks

ID type : ☒ Entrez ID ☐ Symbol

Species : *Mus musculus (Mouse)*

Reset

Search

| No | Accession | Title | Download |
|---------|-----------|---|--------------------------|
| Summary | | | |
| 1 | GSE12420 | Gene profiling of heart atria in PI3K and Mst1 mouse models | Download |
| 2 | GSE1479 | C57BL/6 Benchmark Set for Early Cardiac Development | Download |
| 3 | | <p>Timed matings were performed using C57BL/6 mice and pregnant females sacrificed starting at embryonic day (E) 10.5, and then in daily intervals until E14.5. Gene expression was be further analyzed at E16.5 and E18.5, to monitor changes in gene expression related to maturation of the heart. At stage 10.5, the rostral and caudal parts of the embryo were removed and the middle part, which includes the heart, was subjected to expression analysis. From embryonic day 11.5 on, we isolated embryonic hearts and separated the ventricular from the atrial chambers.</p> <p>Keywords = heart</p> <p>Keywords = development</p> <p>Keywords = cardiac</p> <p>Keywords: time-course</p> | |
| 3 | GSE15129 | Coenzyme Q10-dependent gene expression in SAMP1 mice tissues | Download |
| 4 | GSE17478 | Particulate Matter effect on Mouse Model of Cardiac Failure: Lung and Heart Left Ventricle | Download |

1. Choose ID type and species of interest. Networks will be downloaded according to chosen options.
2. Input keywords that want to search, and click search button. If you want to reset search result, please click left reset button.
3. To show summary of experiments, click title.
4. Click '**Download**' button to download each network.

3. Network-search tools

Option 1. Find new members of a pathway based on network direct neighbors (Gene-centric network search)

A. Data Input

Using this tool, users can predict candidate genes of particular pathway by MouseNet V2 for mouse and other 8 vertebrate species.

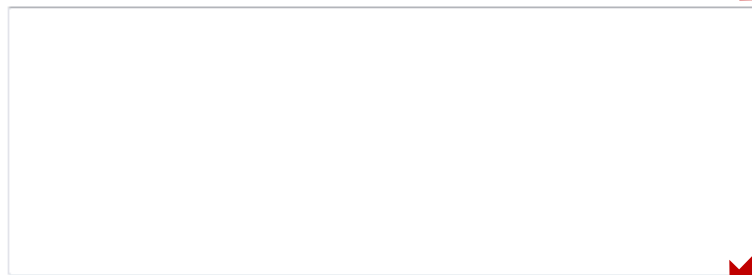
Find new members of a pathway based on network direct neighbors (Pathway-centric network search)

Guide gene Set

Input a set of genes for a function/pathway/phenotype. (Max=500).

Each gene name must be separated by comma, tab, white space or new line.

Input Format : Entrez Gene ID (71950) or Gene Symbol (Nanog)



Organism

Select your organism of interest for the analysis.

MGI Vertebrate Homology is used for converting mouse id to other species. (*Nucl. Acids Res.* (28 January 2015) 43 (D1): D726-D736.).

Each analysis takes 1~3 minutes. Please do not click the submit button multiple times.

3 →

An example gene set

#1 41 *Mus musculus* Innate immune response genes. From GO:0045087

#2 34 *Danio rerio* Heart morphogenesis. From GO:0003007

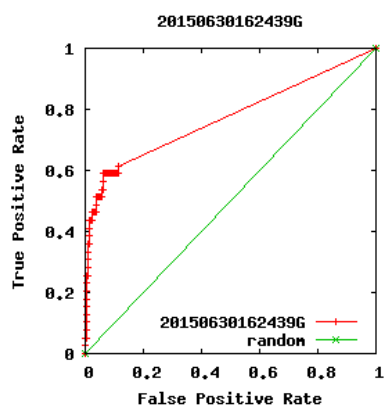
1. Input prior knowledge guide genes of a pathway that a user want to find new candidate genes. Input genes must be official gene symbol or Entrez gene id, and separated by comma, tab, white space or new line.

2. Choose species of interest. Default is *Mus musculus* (mouse).
3. After inputting genes and species, click 'Submit' button to get candidates.
4. If users want to try this tool, use prepared example gene sets.

B. Result page – AUC analysis

Area under ROC curve by 39 guide genes

| total guide genes | valid guide genes in <i>Mus musculus</i> | guide genes in MouseNet V2 | Coverage | AUC | P_value |
|-------------------|--|----------------------------|----------|--------|--------------|
| 41 | 39 | 39 | 1.00 | 0.7724 | 4.030458e-18 |

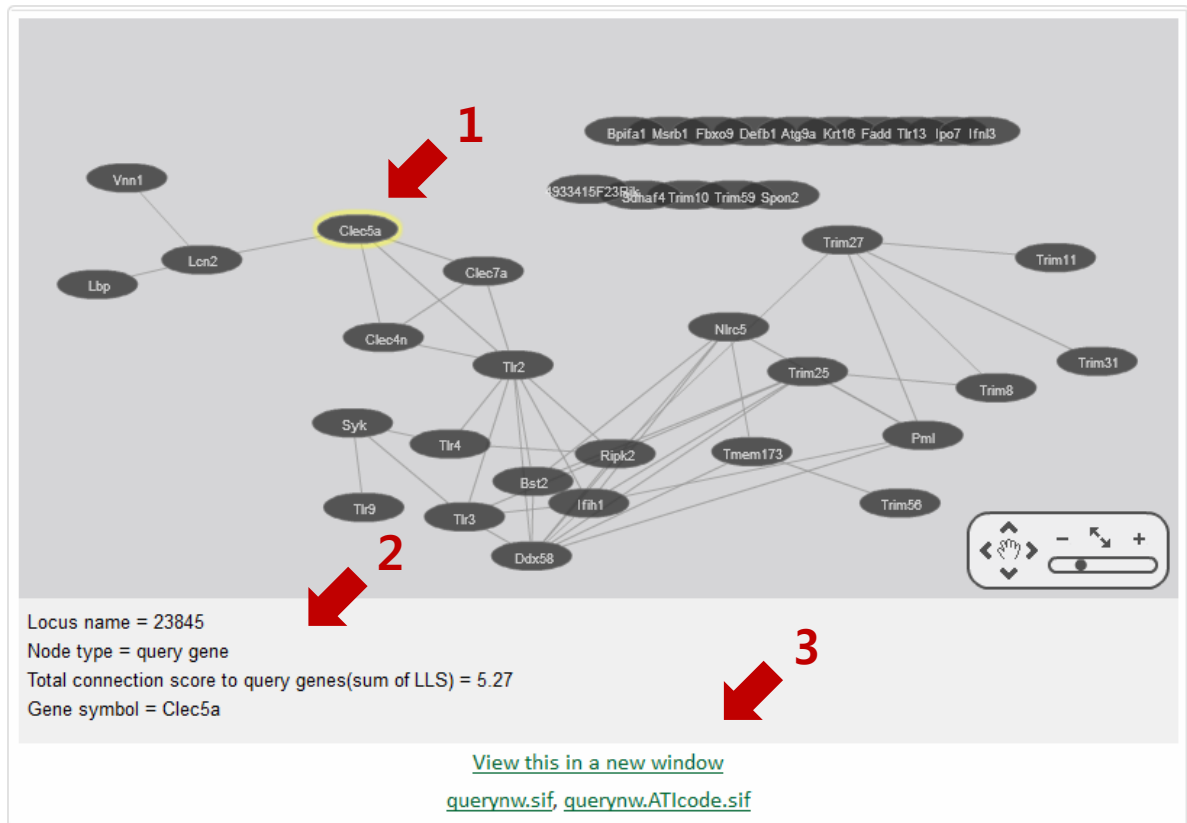


[ROC text file](#)

File format: [False_positive_rate] [True_positive_rate] [Area_under_ROC_curve] with tab delimiters

1. Statistics of query genes. This table shows the number of guide genes input, valid guide genes in *Mus musculus*, guide genes in MouseNet V2, AUC score, and P-value. AUC is 'Area Under ROC Curve' which is shown below and represents closeness of guide genes. Generally, AUC above 0.7 means those genes form closed in MouseNet V2.
2. A plot of ROC analysis. Users can download text file of ROC analysis using the hyperlink below.

C. Result page – Network visualization of guide genes



1. This plot shows network of guide genes using Cytoscape Web. Users can click 'Node' or 'Edge' to show additional information of edges or nodes.
2. Additional information of edges or nodes is shown here.
3. Users can view this graph in a new window, or download Cytoscape Network Files to see the network using [Cytoscape standard alone program](#).

D. Result page – Prioritization of guide genes

Guide genes connected to one another in MouseNet V2 (ranked by total connectivity)

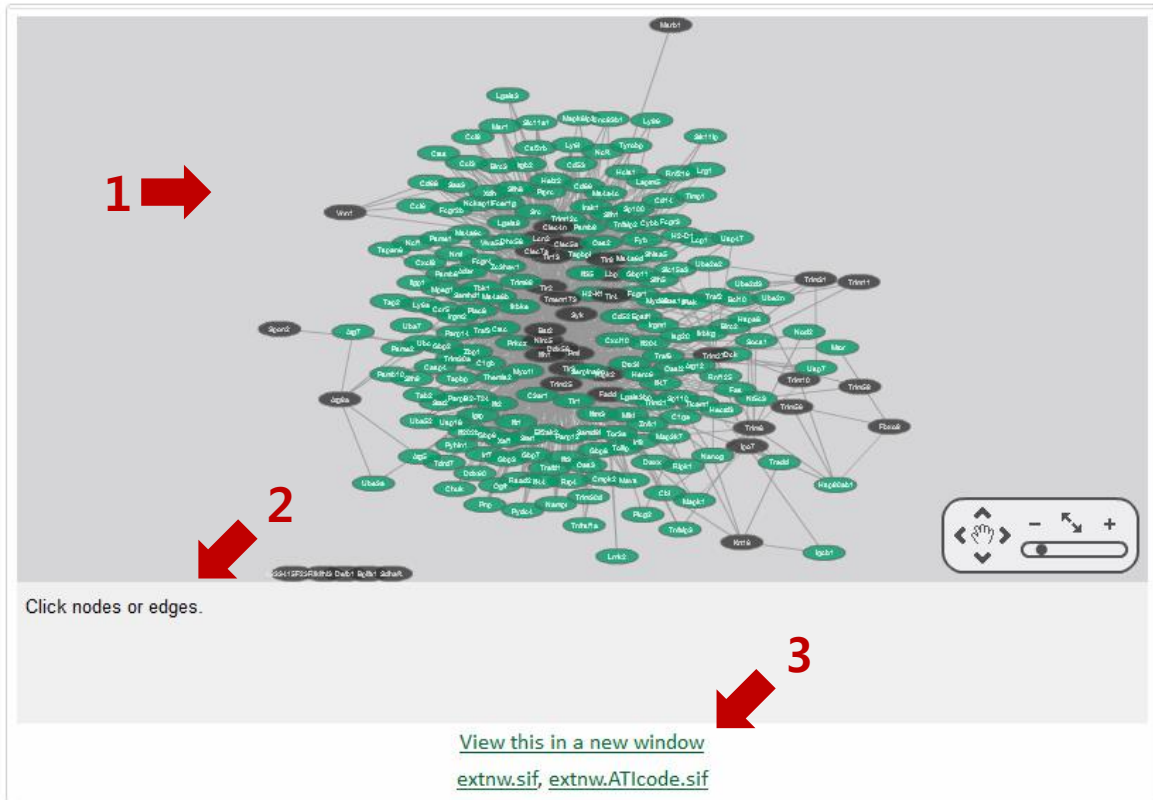
| Rank | Mus musculus gene id | Score | Evidences:Contribution | # connected guide gene / # valid guide gene | Connected guide gene |
|------|-----------------------------------|-------|--|---|---|
| 1 | Ddx58 (230073) | 24.38 | MM-CX:0.52 HS-LC:0.35 MM-LC:0.13 | 9/39 | Tlr3 Pml Ripk2 Trim25 Tlr2 Nlr5 Bst2 Ifih1 Tmem173 |
| | | | | | |
| 2 | Ifih1 (71586) | 16.71 | MM-CX:0.86 HS-LC:0.14 | 7/39 | Tlr3 Pml Trim25 Ddx58 Tlr2 Nlr5 Bst2 |
| | | | | | |

1. This table shows a list of guide genes. Those genes are prioritized using network connectivity scores. Therefore higher rank genes could be considered more important for pathways.

2. MouseNet v2 also presents various pathway terms of genes to provide comprehensive analysis of pathways. Especially, we focused not only mouse phenotypes but also human disease phenotypes to give information of human studies.

E. Result page – Network visualization of new candidates of pathway

New candidate pathway genes associated to 39 valid guide gene(s) in MouseNet V2



1. This plot shows network of new candidates of pathway using Cytoscape Web. Users can click 'Node' or 'Edge' to show additional information of edges or nodes.
2. Additional information of edges of nodes is shown here.
3. Users can view this graph in a new window, or download Cytoscape Network Files to see the network using [Cytoscape standard alone program](#).

F. Result page – A list of new candidates of pathway

| Rank | Mus musculus gene id | Score | Evidences:Contribution | # connected guide gene / # valid guide gene | Connected guide gene |
|---|-----------------------------------|-------|------------------------|--|---|
| Mus musculus GO biological process Human Phenotypes | | | | | |
| 1 | Ms4a6d (68774) | 22.81 | MM-CX:1.00 | 14/39 | Tlr3 Lcn2 Pml Syk Ddx58 Clec5a Tlr2 Tlr13 Nlr5 Clec4n Clec7a Bst2 Ifih1 Tmem173 |
| 2 | Stat1 (20846) | 21.98 | MM-CX:0.67 HS-LC:0.33 | 10/39 | Fadd Tlr3 Pml Ripk2 Syk Trim25 Ddx58 Nlr5 Bst2 Ifih1 |
| <ul style="list-style-type: none"> • Mouse-GOBP: na • Human-GOBP: na • Human-HPO: na • Human-OMIM: na • Human-Phenotype by GWAS catalog: Alzheimer's disease (late onset); Alzheimer's disease; Fibrinogen | | | | | |
| <ul style="list-style-type: none"> • Mouse-GOBP: response to bacterium; cytokine-mediated signaling pathway; lipopolysaccharide-mediated signaling pathway; response to lipopolysaccharide; response to exogenous dsRNA; transcription, DNA-templated; regulation of transcription, DNA-templated; activation of cysteine-type endopeptidase activity involved in apoptotic process; negative regulation of macrophage fusion; interferon-gamma-mediated signaling pathway; type I interferon signaling pathway; cellular response to lipopolysaccharide • Human-GOBP: regulation of transcription from RNA polymerase II promoter; transcription from RNA polymerase II promoter; JAK-STAT cascade; tumor necrosis factor-mediated signaling pathway; positive regulation of transcription, DNA-templated; positive regulation of transcription from RNA polymerase II promoter; interferon-gamma-mediated signaling pathway; negative regulation of endothelial cell proliferation; negative regulation of angiogenesis; cellular response to interferon-beta; negative regulation of I-kappaB kinase/NF-kappaB signaling; endothelial cell migration; positive regulation of transcription from RNA polymerase II promoter; negative regulation by virus of viral protein levels in host cell; renal tubule development; cytokine-mediated signaling pathway; regulation of apoptotic process; interferon-gamma-mediated signaling pathway; regulation of interferon-gamma-mediated signaling pathway; type I interferon signaling pathway; regulation of type I interferon-mediated signaling pathway; JAK-STAT cascade involved in growth hormone signaling pathway • Human-HPO: Puberty and gonadal disorders;Hyperkeratosis;Diabetes mellitus;Inflammatory abnormality of the skin;Diarrhea;Abnormal leukocyte count;Skin ulcer;Hematuria;Idiopathic myelofibrosis;Anemia due to reduced life span of red cells;Hemolysis | | | | | |

1. This table shows a list of new candidates of input pathway. Those genes are prioritized using network connectivity scores. Therefore higher rank genes could be considered more important for pathways.

2. We also present various pathway terms of genes to provide comprehensive analysis of pathways. Especially, we focused not only mouse phenotype but also human disease phenotype to give information of connection with human study.

G. Result page – Gene set analysis with guide genes using Gene Ontology.

GeneSet Analysis using Gene Ontology

You can run GeneSet Analysis for only 24 connected query genes below!

230073, 71586, 24088, 217069, 434341, 18854, 69550, 192656, 19720, 142980, 20963, 21898, 72512, 23845, 56644, 56620, 16819, 93679, 384309, 16803, 81897, 94091, 224762, 22361

You can run GeneSet Analysis for all query genes in MouseNet V2 (valid query genes) below!

230073, 71586, 24088, 217069, 434341, 18854, 69550, 192656, 19720, 142980, 20963, 21898, 72512, 23845, 56644, 56620, 16819, 93679, 384309, 16803, 81897, 94091, 224762, 22361, 100689, 13214, 14082, 16666, 18843, 19824, 233726, 245860, 27361, 279572, 338374, 66755, 66949, 68002, 71538

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|--------|-------|-------|--------|--------|-------|-------|--------|-------|--------|-------|-------|-------|-------|-------|-------|-------|-------|--------|-------|-------|-------|--------|-------|--------|-------|-------|-------|-------|-------|--------|--------|-------|--------|--------|-------|-------|-------|-------|
| 230073 | 71586 | 24088 | 217069 | 434341 | 18854 | 69550 | 192656 | 19720 | 142980 | 20963 | 21898 | 72512 | 23845 | 56644 | 56620 | 16819 | 93679 | 384309 | 16803 | 81897 | 94091 | 224762 | 22361 | 100689 | 13214 | 14082 | 16666 | 18843 | 19824 | 233726 | 245860 | 27361 | 279572 | 338374 | 66755 | 66949 | 68002 | 71538 |
|--------|-------|-------|--------|--------|-------|-------|--------|-------|--------|-------|-------|-------|-------|-------|-------|-------|-------|--------|-------|-------|-------|--------|-------|--------|-------|-------|-------|-------|-------|--------|--------|-------|--------|--------|-------|-------|-------|-------|

Submit

1. For run gene set analysis, copy genes of above into the box. Default list is valid query genes.
2. Click submit button.

Option 2. Infer function from network neighbors (Pathway-centric network search).

A. Data input

Infer function from network neighbors (Gene-centric network search)

Functional annotations

Mouse-GOBP : Gene Ontology Biological Process (Mouse)
Mouse-KEGG : Kyoto Encyclopedia of Genes and Genomes (Mouse)
Mouse-MP : Mammalian Phenotype (Mouse)
Human-GOBP : Gene Ontology Biological Process (Human)
Human-OMIM : Online Mendelian Inheritance in Man (Human)
Human-HPO : The Human Phenotype Ontology (Human)

Mouse-GOBP Annotation Evidence Code (optional)
Choose GO Annotation Evidence Code Filters.
Default 6 evidence codes are with high reliability.

1 → ☒ IDA ☒ IMP ☒ IGI ☒ IPI ☒ IEP ☒ TAS
☐ RCA ☐ IGC ☐ ISS ☐ NAS ☐ IEA ☐ IC

Gene Set
Input a set of genes for a function/pathway/phenotype. (Max=300).
Each gene name must be separated by comma, tab, white space or new line.
Input Format : Entrez Gene ID (71950) or Gene Symbol (Nanog)

2 →

3 → **Organism**
Select your organism of interest for the analysis.
MGI Vertebrate Homology is used for converting mouse id to other species.
(*Nucl. Acids Res.* (28 January 2015) 43 (D1): D726-D736.).

4 →

Example gene sets

#1 3 mouse genes unannotated by GOBP: Adam4, Scgn, Synpo2
#2 rfx2 (known for ciliogenesis in *Xenopus*) ([Chung et al., 2012](#))

5 →

1. (Optional) Choose Mouse GOBP annotation evidence codes that will be used in this tool. Evidences in upper line represent experimentally validated annotation and evidences in lower line represent computationally generated annotation. Detail information of codes is described in the next page.

2. Input genes into the box. Input genes must be official gene symbol or Entrez gene id, and separated by comma, tab, white space or new line.

3. Choose species of interest. Default is *Mus musculus* (mouse).

- After input genes and species, click 'Submit' button to get candidates.
- If users want to try this tool, use example gene sets.

| GO evidence code | Description by Gene Ontology |
|------------------|---|
| IDA | Inferred from Direct Assay |
| IMP | Inferred from Mutant Phenotype |
| IGI | Inferred from Genetic Interaction |
| IPI | Inferred from Physical Interaction |
| IEP | Inferred from Expression Pattern |
| TAS | Traceable Author Statement |
| RCA | Inferred from Reviewed Computational Analysis |
| IGC | Inferred from Genomic Context |
| ISS | Inferred from Sequence or Structural Similarity |
| NAS | Non-traceable Author Statement |
| IEA | Inferred from Electronic Annotation |
| IC | Inferred by Curator |

B. Result page

Infer function from network neighbors (Gene-centric network search)

Top 30 functional annotation terms are summarized in tables for each gene.

Indexes (Official_Symbol(Entrez ID))

| | | |
|------------------|------------------|--------------------|
| Adam4 (11498) | Scgn (214189) | Synpo2 (118449) |
|------------------|------------------|--------------------|

Entrez ID: 11498 Symbol: Adam4

| Rank | Mouse-GOBP | Mouse-KEGG | Mouse-MP | Human-GOBP | Human-OMIM | Human-HPO |
|------|---|----------------------------------|-------------------------------------|--|---|--|
| 1 | binding of sperm to zona pellucida | Endocytosis | abnormal fertilization | binding of sperm to zona pellucida | Inflammatory skin and bowel disease,neonatal,1 (614328) | Thick nail |
| 2 | membrane protein ectodomain proteolysis | Notch signaling pathway | abnormal mitral valve morphology | multicellular organism reproduction | Codeine sensitivity (608902) | Inflammatory abnormality of the skin |
| 3 | prevention of polyspermy | Alzheimer's disease | ventricular septal defect | single fertilization | Debrisoquine sensitivity (608902) | Leukocytosis |
| 4 | single fertilization | Serotonergic synapse | abnormal pulmonary valve morphology | extracellular matrix disassembly | Agnathia-otocephaly complex (202650) | Erythroderma |
| 5 | proteolysis | Steroid hormone biosynthesis | abnormal semilunar valve morphology | extracellular matrix organization | Epilepsy,progressive myoclonic 5 (613832) | Internal hemorrhage |
| 6 | adult behavior | Protein digestion and absorption | abnormal tricuspid valve morphology | central nervous system development | | Functional abnormality of the gastrointestinal tract |
| 7 | cell adhesion | Wnt signaling pathway | abnormal aortic valve morphology | epidermal growth factor receptor signaling pathway | | Erythema |

- Genes inferred functions from network neighbor's functional annotation terms is shown as boxes. Click the box of a gene that users want to see. In this figure, Adam4 is checked.
- Information of the input gene. Gene id, symbol, and GO-BP terms of the gene are present here.
- A list of inferred functions from network neighbor's functional annotation terms is described as

a table. The rank of term was measured based on sum of LLS of neighbors who have that functional annotation term. Although Adam4 is completely unannotated by GOBP, first annotation term predicted by Mouse-GOBP (binding of sperm to zona pellucida) is validated by experimental results from the literature (Cecil Han et al., 2009). Each table shows top 30 functional annotation terms.

4. Hypothesis generation process

- I want to find new genes of particular pathway or phenotype.

1. Gather prior knowledge (genes) of the pathway.
2. Input those genes in '**Gene prioritization based on network direct neighborhood**' tool in Network-search menu.
3. See '**New candidates pathway genes**' section of the result page.
4. Experimentally validates those new candidates.

- I want to know functions of unknown genes

1. Input those genes in '**Infer functions from network neighbors**' tool in Network-search menu.
2. Analyze new functions of genes.

- I want to know a hub gene in particular pathway.

1. Gather genes of the pathway.
2. Input those genes in '**Gene prioritization based on network direct neighborhood**' tool in Network-search menu.
3. See '**Guide genes connected to one another in MouseNet V2**' section of the result page.
4. High ranked genes could be considered hub genes of the pathway.