

PICKLE 3 Manual

The web interface of PICKLE (www.pickle.gr), described in detail in Gioutlakis et al., 2017, has been updated to include the ability to search the mouse PPI database. Modifications have been applied to all three parts of the interface: i. the entity identification and interaction querying section; ii. the PPI result section, and iii. the network visualization section.

i. The entity identification and interaction querying section

In the upgraded version, the user has now the option to search either the human or the mouse PPI meta-database, using human or mouse, respectively, genetic entity identifiers (Suppl. Fig. 2). The rest of the section has the same structure as in PICKLE 2.0 for both species.

Specifically, the user can query for one or multiple protein entries, using a variety of identifier types, i.e. UniProt accession, UniProt entry name, UniProt isoform, UniProt name, RefSeq nucleotide accession, RefSeq protein accession, ENA nucleotide accession, Gene symbol, Gene name, Gene locus, GenBank GeneID, Ensembl GeneID, GO terms. Then, the system maps those identifiers to entities of the PICKLE RHCP or RMCP genetic information ontology network, respectively, for the human or mouse meta-database, and returns the candidate list to the user for review. Having selected at least one entity from the list, the user can proceed and set the PPI search criteria, namely: (a) the PICKLE network normalization level (i.e. protein (UniProt) or Gene), (b) the PICKLE network filtering mode, i.e. none, standard or cross-checking (default), and (c) the PPIs that the system will retrieve from the respective PICKLE network. Currently, the user can search for: (i) the interactions of the queried biological entities, retrieving thus their “first neighbors”, or (ii) the interactions of the queried entities and any interactions that may exist between those first neighbors, or (iii) the interactions, if any, exclusively between the queried entities.

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Search Selection of human or mouse PICKLE

Select species: Mouse notch1

Search for the identifier(s) in the PICKLE RHCP/RMCP ontology network

Identified interactors

| Gene ID | Symbol | Gene Name | Uniprot Accession | Entry name | Protein Name | Match |
|---|--------|-----------|-------------------|-------------|--|-------------------------------------|
| <input checked="" type="checkbox"/> 18128 | Notch1 | notch 1 | Q01705 | NOTC1_MOUSE | Neurogenic locus notch homolog protein 1 | Primary match: gene symbol = notch1 |

Search for PPIs

Normalization level: Protein (UniProt) Gene

Filtering method: Cross-checking (default)

Network setup: First neighbors

Find Interactions

Supplementary Figure 2. The entity identification and interaction querying section of the updated PICKLE web interface. The user can now query either the human or the mouse meta-database. The mouse protein Notch1 is used as example.

ii. The PPI result section

In the mouse PICKLE, the PPI result section has been modified compared to the respective section in the human PICKLE, as described in Gioutlakis et al. 2017, to accommodate both the $PPI_{(m-m)}$ and $PPI_{(m-h)}$ subnetworks and the mouse-human genetic entity orthology links (Suppl. Fig. 3). More specifically, for any queried mouse genetic entity, the resulting interactions identified in the $PPI_{(m-m)}$ subnetwork are shown in the first (upper) part of the result section (Part A), formatted in such a way that queried mouse entities are shown as first interactors. If the queried mouse entities have also human interactors, then these $PPI_{(m-h)}$ are shown in the second (middle) part of the result section (Part B), separated by a straight line from Part A. Moreover, if the queried mouse genetic entities have human orthologs, then the interactions of the latter, if any, with mouse entities are also shown in this $PPI_{(m-h)}$ part of the result section. These interactions are formatted with the human orthologs of queried mouse entities as the first interactor. Finally, the last (bottom) part of the result section (Part C) comprises any mouse-human ortholog pairs involved in the retrieved interaction network for the queried mouse entities.

Identified Interactions

(sorted by their cross-checked confidence score, their standard confidence score and the number of their supporting publications)

28 interactions

[Download results](#) [Visualize results](#)

Upper part: PPIs between mouse entities, middle part: PPIs between mouse-human entities, bottom part: ortholog human-mouse gene pairs
 Linked PPI: "yes" if at least one corresponding by orthology PPI exists in the retrieved dataset
 Human PPI: "yes"/"no" indicates if a corresponding by orthology PPI exists in human PICKLE, blank if at least one entity has no human ortholog

| InteractorA | InteractorB | Linked PPI | Sources | Cross-Checked Confidence | Standard Confidence | Pub. no | Publications | Link | Human PPI |
|-------------|-------------|------------|-----------------|--------------------------|---------------------|---------|-------------------|---------|-----------|
| NOTC1_MOUSE | RS27A_MOUSE | | DIP, IntAct | 2 | 2 | 2 | 21124883 25344755 | details | yes |
| NOTC1_MOUSE | RL40_MOUSE | | DIP, IntAct | 2 | 2 | 2 | 21124883 25344755 | details | |
| NOTC1_MOUSE | SMCA4_MOUSE | | DIP, IntAct | 2 | 2 | 1 | 17210915 | details | yes |
| NOTC1_MOUSE | SMRD3_MOUSE | | BioGRID, IntAct | 2 | 2 | 1 | 17210915 | details | no |
| NOTC1_MOUSE | KAT2B_MOUSE | yes | BioGRID | 2 | 2 | 1 | 10747963 | details | yes |
| NOTC1_MOUSE | KAT2A_MOUSE | yes | BioGRID | 2 | 2 | 1 | 10747963 | details | yes |
| NOTC1_MOUSE | WDR12_MOUSE | | BioGRID | 2 | 2 | 1 | 11827460 | details | yes |
| NOTC1_MOUSE | DLL1_MOUSE | | BioGRID | 2 | 2 | 1 | 21985982 | details | yes |
| NOTC1_MOUSE | NUMB_MOUSE | yes | BioGRID | 2 | 2 | 1 | 20844536 | details | yes |
| NOTC1_MOUSE | PSN2_MOUSE | | BioGRID | 2 | 2 | 1 | 11518718 | details | yes |
| NOTC1_MOUSE | EGFL7_MOUSE | yes | BioGRID | 2 | 2 | 1 | 19503073 | details | yes |
| NOTC1_MOUSE | SUH_HUMAN | yes | BioGRID, IntAct | 2 | 2 | 2 | 19503073 21102556 | details | yes |
| NOTC1_MOUSE | SMAD3_HUMAN | | IntAct | 2 | 2 | 1 | 14638857 | details | yes |
| NOTC1_MOUSE | PSN1_HUMAN | | DIP, IntAct | 2 | 2 | 1 | 21115843 | details | yes |
| NOTC1_MOUSE | KAT2B_HUMAN | yes | BioGRID | 2 | 2 | 1 | 10747963 | details | yes |
| NOTC1_MOUSE | KAT2A_HUMAN | yes | BioGRID | 2 | 2 | 1 | 10747963 | details | yes |
| NOTC1_MOUSE | NUMB_HUMAN | yes | BioGRID | 2 | 2 | 1 | 21356309 | details | yes |
| NOTC1_MOUSE | GRAB_HUMAN | | BioGRID | 2 | 2 | 1 | 16798735 | details | |
| NOTC1_MOUSE | XIAP_HUMAN | | BioGRID | 2 | 2 | 1 | 17318174 | details | yes |
| NOTC1_MOUSE | EGFL7_HUMAN | yes | BioGRID | 2 | 2 | 1 | 19503073 | details | yes |
| NOTC1_MOUSE | M3K7_HUMAN | | BioGRID | 2 | 2 | 1 | 29228365 | details | |
| NOTC1_MOUSE | TRAF6_HUMAN | | BioGRID | 2 | 2 | 1 | 29228365 | details | no |
| NOTC1_HUMAN | FBXW7_MOUSE | | DIP, IntAct | 2 | 2 | 1 | 25344755 | details | yes |
| NOTC1_HUMAN | ITCH_MOUSE | yes | BioGRID | 2 | 2 | 1 | 18628966 | details | yes |
| DLL1_HUMAN | DLL1_MOUSE | | Orthology (MGI) | | | | | | |
| EGFL7_HUMAN | EGFL7_MOUSE | | Orthology (MGI) | | | | | | |
| FBXW7_HUMAN | FBXW7_MOUSE | | Orthology (MGI) | | | | | | |

Supplementary Figure 3. The mouse PICKLE result section. Parts A and B show, respectively, the retrieved interactions in the $PPI_{(m-m)}$ and $PPI_{(m-h)}$ subnetworks, while Part C shows the involved mouse-human ortholog pairs. The depicted example concerns the first neighbors of mouse protein Notch in the PICKLE 3.0 (release 1) cross-checked (default) mouse PPI network at the protein (UniProt) level (Suppl. Fig 2).

In Parts A and B, the interactions are sorted based on their cross-checked confidence score, their standard confidence score and the total number of supporting publications, the links to which are also provided. By clicking “details”, the user can retrieve the source information about the identified PPIs as this is recorded in the primary datasets. Another modification in mouse compared to the human PICKLE is the addition of the columns “Linked PPI” positioned immediately after the interactors and “Human PPI” appearing last. The “Linked PPI” column of an interaction is empty, if the interaction does not have any other corresponding through ontology PPI in the resulting set and “yes”, otherwise. If the user clicks on the “yes” value of an interaction in Part A, the system refers him/her to its corresponding interaction(s) in Part B and vice versa. The “Human PPI” column of a $PPI_{(m-m)}$ or $PPI_{(m-h)}$ is of value “yes” or “no”, when the corresponding through orthology $PPI_{(h-h)}$ does or does not, respectively, exist, in the human PICKLE. If one or both of the mouse interactors do

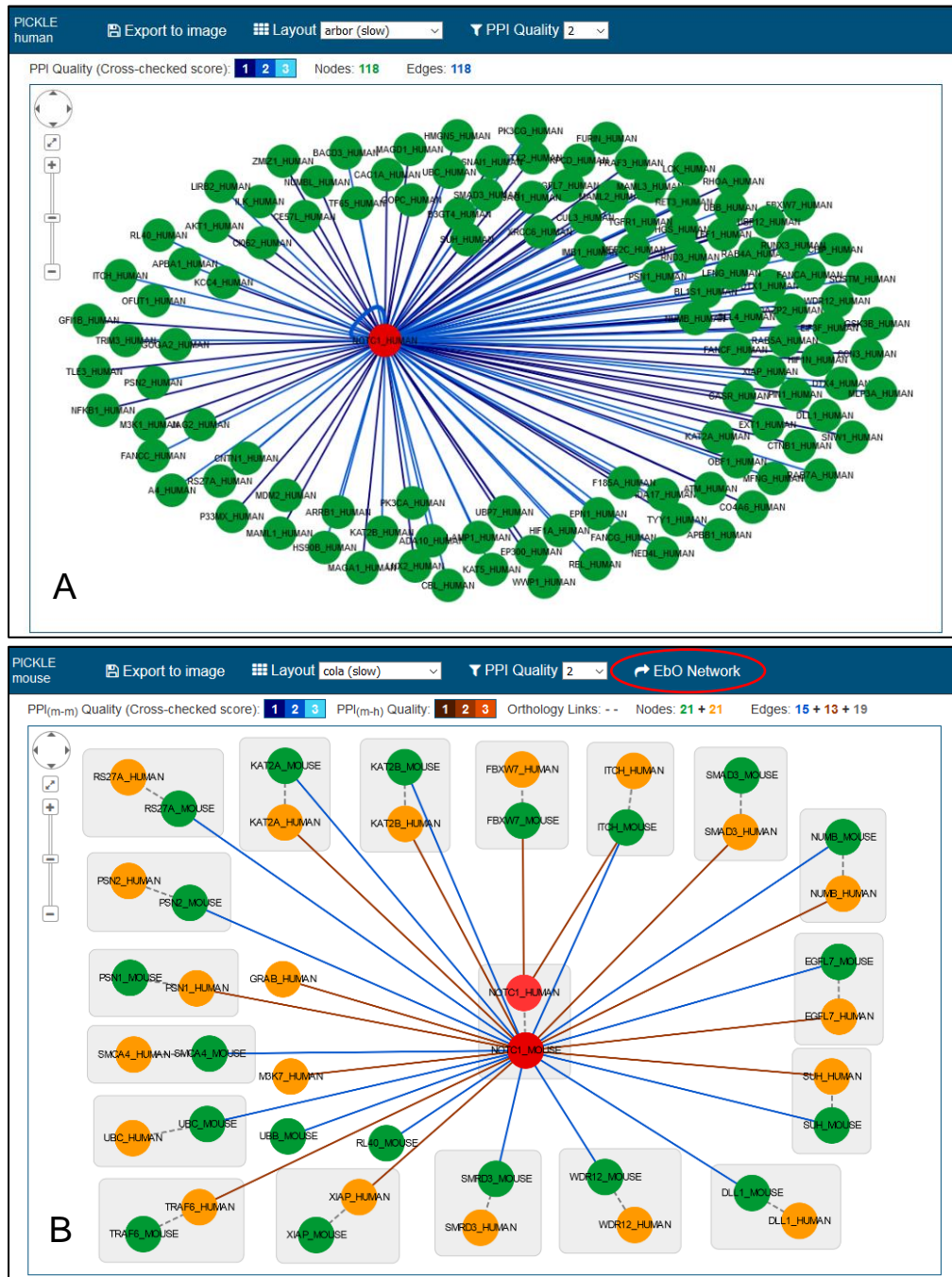
not have human orthologs in the utilized ortholog pair list (Suppl. File 1B), direct inference of the corresponding $PPI_{(h-h)}$ presence is not possible and the “Human PPI” column is empty.

The user can download the resulting PPI set in a tab-delimited format and/or visualize it (if size permits). The downloadable .txt file contains an additional column to the online result section, which includes the PICKLE ID of each interaction (appearing as first column of the file), while the non-empty “Linked PPI” columns contain the ID(s) of the corresponding through orthology interactions of the respective PPIs.

iii. The network visualization section

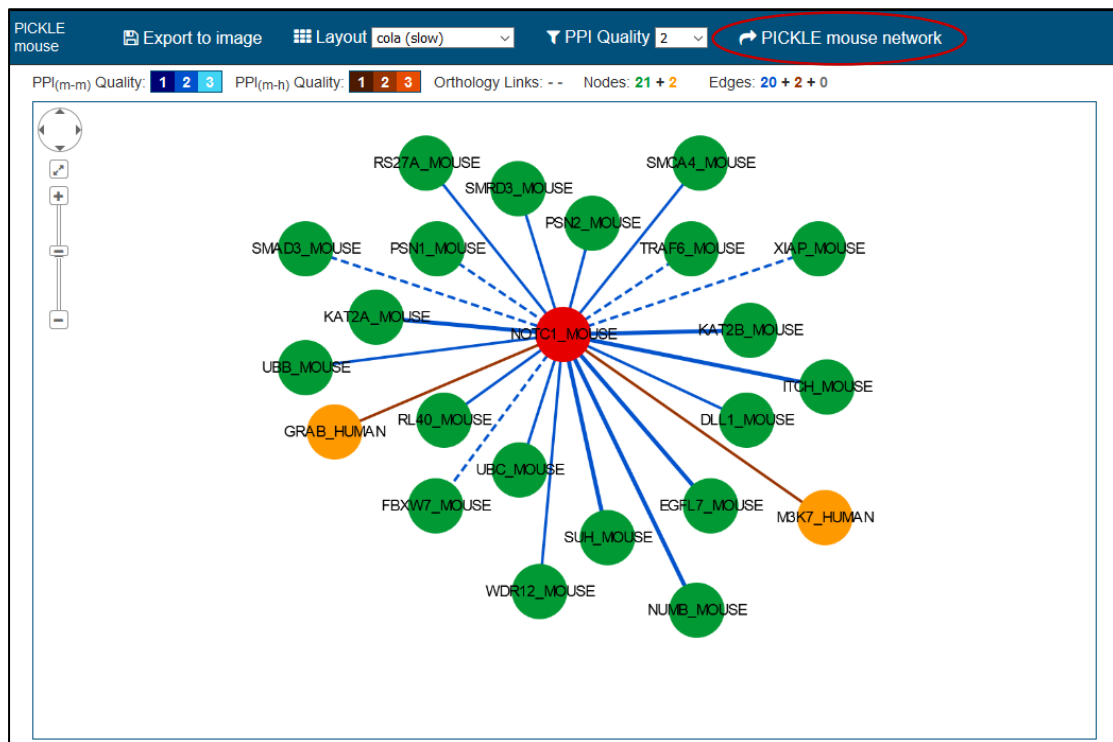
The network visualization page has been updated to Cytoscape.js (Franz et al., 2015). In addition, the user can now select between six different network layouts, with “cola” used as the default, and export the visualized network as image file (Suppl. Fig. 4). By default, the nodes representing proteins of the main species (i.e. human or mouse in the respective PICKLE) are depicted as green circles and only the queried protein nodes as red. Interactions are shown in different shades of blue depending on their confidence score. The user can select to see only the PPIs of a certain cross-checked confidence score and above. In the mouse PICKLE, the human protein nodes are depicted as orange circles to differentiate them from the default mouse protein nodes. The edges between mouse and human genetic entities are colored in different shades of brown depending on their confidence score. Furthermore, apart from the queried mouse protein nodes, their human ortholog nodes, if existed, are shown in red, too. Finally, the nodes of the mouse-human ortholog pairs are shown in a rectangular, connected through a dashed gray line. At the right top of the visualization window, the user can see some basic network statistics. In the case of human PICKLE (Suppl. Fig. 4A), these include the number of human protein nodes (green fonts) and the number of PPIs (blue fonts). In the case of mouse PICKLE (Suppl. Fig. 4B), the number of nodes in green fonts represents the number of mouse proteins (default species), augmented by the number of human protein nodes in orange fonts. Accordingly, for the edges, the user can see the number of $PPI_{(m-m)}$, $PPI_{(m-h)}$ and mouse-human ortholog pairs/links in blue, brown and gray fonts, respectively. In mouse PICKLE, the user can also visualize the queried PPI network within the mouse

EbO interactome, by clicking on the respective button in the menu bar of the original visualization window (Suppl. Fig 4B).



Supplementary Figure 4. The experimentally determined PPI network visualization window in human (A) and mouse (B) PICKLE. The depicted examples concern the first neighbors of human protein NOTCH1 (A) and mouse protein Notch1 (B) in the PICKLE 3.0 (release 1) cross-checked (default) PPI network at the protein (UniProt) level. In mouse PICKLE, the user has the option to visualize the queried PPI network in the EbO interactome by clicking on the respective button in the menu bar of the visualization window (in red circle).

In the EbO visualization window of mouse PICKLE (Suppl. Fig 5), the potentially valid $PPI'_{(m-m)}$ (types 3' and 5' in Fig. 1, main text) are shown as dashed blue lines. In addition, a $PPI_{(m-m)}$ with one or two corresponding through orthology $PPI_{(m-h)}$ is depicted with a thicker straight blue line in the EbO network. Similarly, a $PPI'_{(m-m)}$ predicted by two corresponding by orthology $PPI_{(m-h)}$ is shown with a thicker dashed blue line. The user can refer to the experimentally determined PPI network in the original visualization window by clicking on the respective button of the EbO visualization window.



Supplementary Figure 5. The EbO PPI network visualization window in mouse PICKLE. The example shows the first neighbors of mouse protein Notch1 in the PICKLE 3.0 (release 1) cross-checked (default) EbO network at the protein (UniProt) level, corresponding to the experimentally determined network shown in Suppl. Fig. 4B. The user can return to the original visualization window by clicking on the respective button in the menu bar (in red circle).

References

Franz, M., et al. (2015). Cytoscape.js: a graph theory library for visualisation and analysis. *Bioinformatics*, 32(2), 309-311.