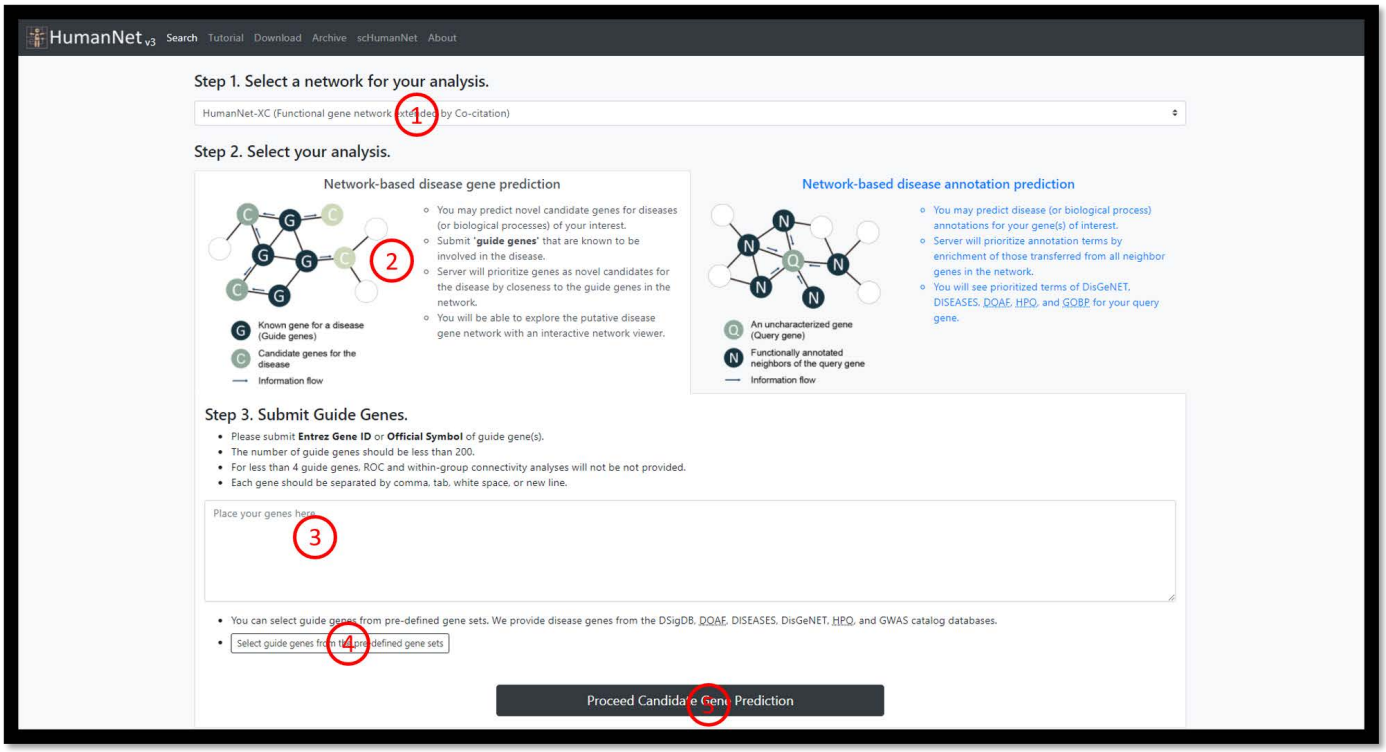
HumanNet v3 Tutorial

INDEX

1. Network-based candidate gene prediction.

Predicting new candidate genes for your diseases (or biological processes) of interest can be accomplished by exploiting direct linkages of HumanNet. To predict candidate genes, submit a set of genes that are known to be involved in the disease. These submitted genes are used as 'guide genes' to search for novel candidate genes. The predicted candidate genes are prioritized by summing the edge scores that are directly connected to guide genes. Highly ranked candidate genes are potentially new members of the disease.

1-1. Gene submission form.



① Select a network for your analysis.

- You can select a network among 2-tier model of HumanNet.
- **HumanNet-XC (default):** Extended network by co-citation.
- **HumanNet-FN:** Functional gene network.
- **HumanNet-PI:** Protein-protein interaction network

HumanNet-XC (18,462 genes; 1,125,494 links)
(Extended gene network by co-citation)

- **CC** Co-functional links by co-citation

HumanNet-FN (18,459 genes; 977,495 links)
(Functional gene network)

- **CX** Co-functional links by co-expression
- **DB** Co-functional links by pathway database
- **DP** Co-functional links by domain profile association
- **GI** Co-functional links by genetic interaction
- **GN** Co-functional links by gene neighborhood
- **PG** Co-functional links by phylogenetic profile association

HumanNet-PI (17,849 genes; 633,460 links)

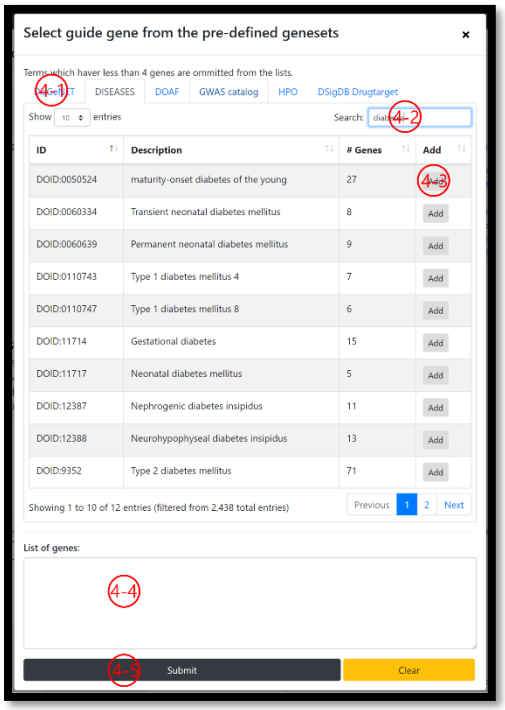
- **PI** Protein-protein interaction network

② Click “Network-based candidate gene prediction” for candidate gene prediction.

③ Submit your guide genes here.

- Guide genes: A set of genes that are known to be involved in the disease of interest.
- Please submit Entrez Gene ID or Official Symbol of guide gene(s).
- The number of guide genes should be less than 200.
- For less than 4 guide genes, ROC and within-group connectivity analyses will not be not provided.
- Each gene should be separated by comma, tab, white space, or new line.

④ You can submit pre-defined genes of your diseases of interest.



(4-1) You can choose a database to get pre-defined disease genes. HumanNet provides DisGeNET, DISEASES, DOAF, GWAS catalog, HPO, and DSigDB databases.

(4-2) You can search a disease of your interest.

(4-3) Click ‘add’ button to add pre-defined disease genes.

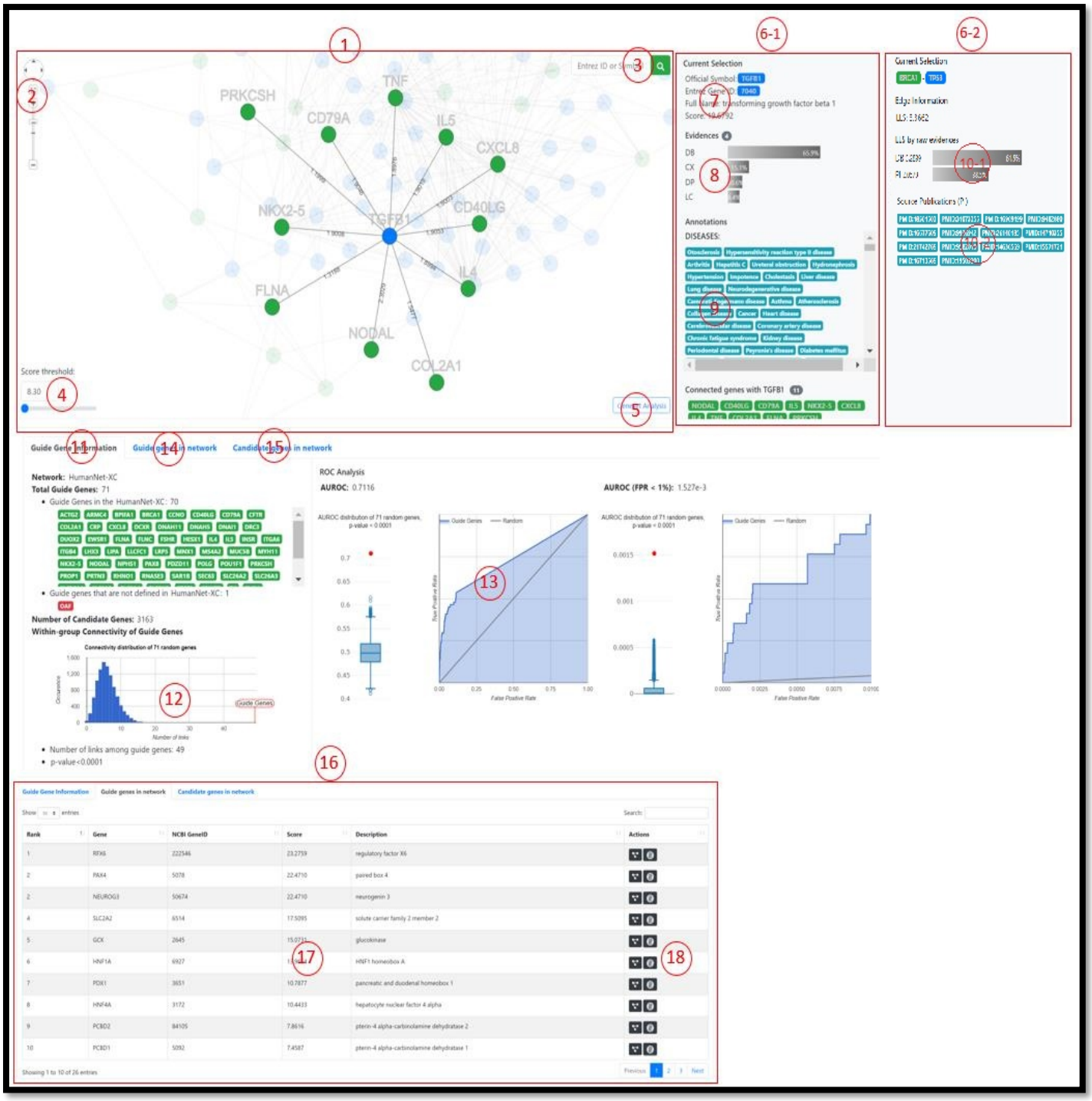
(4-4) The pre-defined disease genes will be appeared here when you click the ‘add’ button, you can also edit to finalize the gene list.

(4-5) Click ‘submit’ button to submit the genes.

⑤ Click to proceed the analysis with your gene list.

- The analysis may take 1~2 minutes. Please do not click the submit button multiple times.

1-2. Candidate gene prediction result



① You can explore guide genes and candidate genes in the network view panel.

- All the guide genes that you submitted and top 100 candidate genes will be shown in the view.
- If nothing is shown on the view, please refresh the page. (F5 or refresh button)

- You can see edges among guide genes and edges between guide genes and candidate genes in the view. (edges between candidate genes are not shown in the view)
- You can highlight a node or an edge by clicking it.

② Network view control panel.

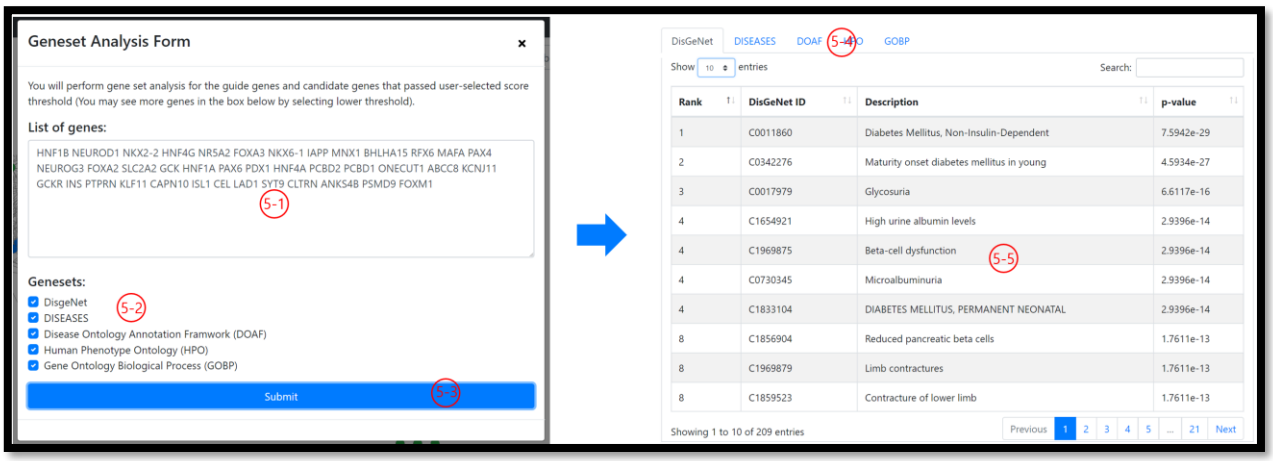
- Move the screen.
- Focus the network.
- Vertical bar: Zoom in or out.

③ You can search and highlight a gene of interest.

④ Score threshold for the candidate genes.

- All the guide genes will be shown regardless of the threshold.
- Candidate genes with a score lower than the threshold will not be displayed in the network view panel.
- You can see all the guide genes and the candidate genes by setting the threshold to the lowest.
- By setting the threshold to the highest, you can explore only the guide genes.

⑤ You can investigate the enriched diseases of the genes on current view.



(5-1) Genes in the current view will be automatically filled in the text box.

(5-2) You can select the disease annotation databases for the analysis.

(5-3) Click to proceed gene set analysis

(5-4) Select a disease annotation database.

(5-5) The enriched terms are shown in the table, p-values are calculated by fisher's exact test.

⑥ You can see the information of the selected gene or edge on this panel.

(6-1) Selection panel when you select a gene.

(6-2) Selection panel when you select an edge.

⑦ Supporting evidence of the selected gene. It represents the contribution of each evidence when the selected gene got scores from the neighboring guide genes.

⑧ Functional annotation of the selected gene. (by GOBP)

⑨ Neighboring genes of the selected gene.

- Strongly connected genes are shown at the front.
- When you select a guide gene, you can see all the neighbors of the guide gene.
- When you select a candidate gene, you can see the neighboring guide genes.

⑩ Information of the selected edge

(10-1) Supporting evidences and contribution of the edge.

(10-2) Supporting publication. This information is only available for PI, CC, and a part of GI links.

If you click the PMID of interest, you can browse corresponding publication

⑪ General information tab contains information and closeness analysis of the guide genes.

⑫ Within-group connectivity analysis result.

- Blue histogram represents the distribution of link count among random genes (same number with total guide genes. 10,000 iterations)
- The farther the guide gene annotation is located from the random distribution, the more significant their connection is.

⑬ ROC curve and the corresponding AUC (Area Under ROC curve).

- Box plot represents the distribution of null AUROC calculated from 10,000 random genes with same guide gene size.
- We also provide early retrieved AUROC which is obtained by calculating the area under ROC curve while FPR reaches to 0.01 (1%).
- Early retrieved AUROC (FPR < 1%) represent the prediction power of candidate genes in top ranks.

⑭ You can see the information of the guide genes.

⑮ You can see the information of the candidate genes.

⑯ This panel will be shown when you click the button ⑭ or ⑮.

⑰ In the table, you can examine the guide genes (or candidate genes) sorted by the score they got.

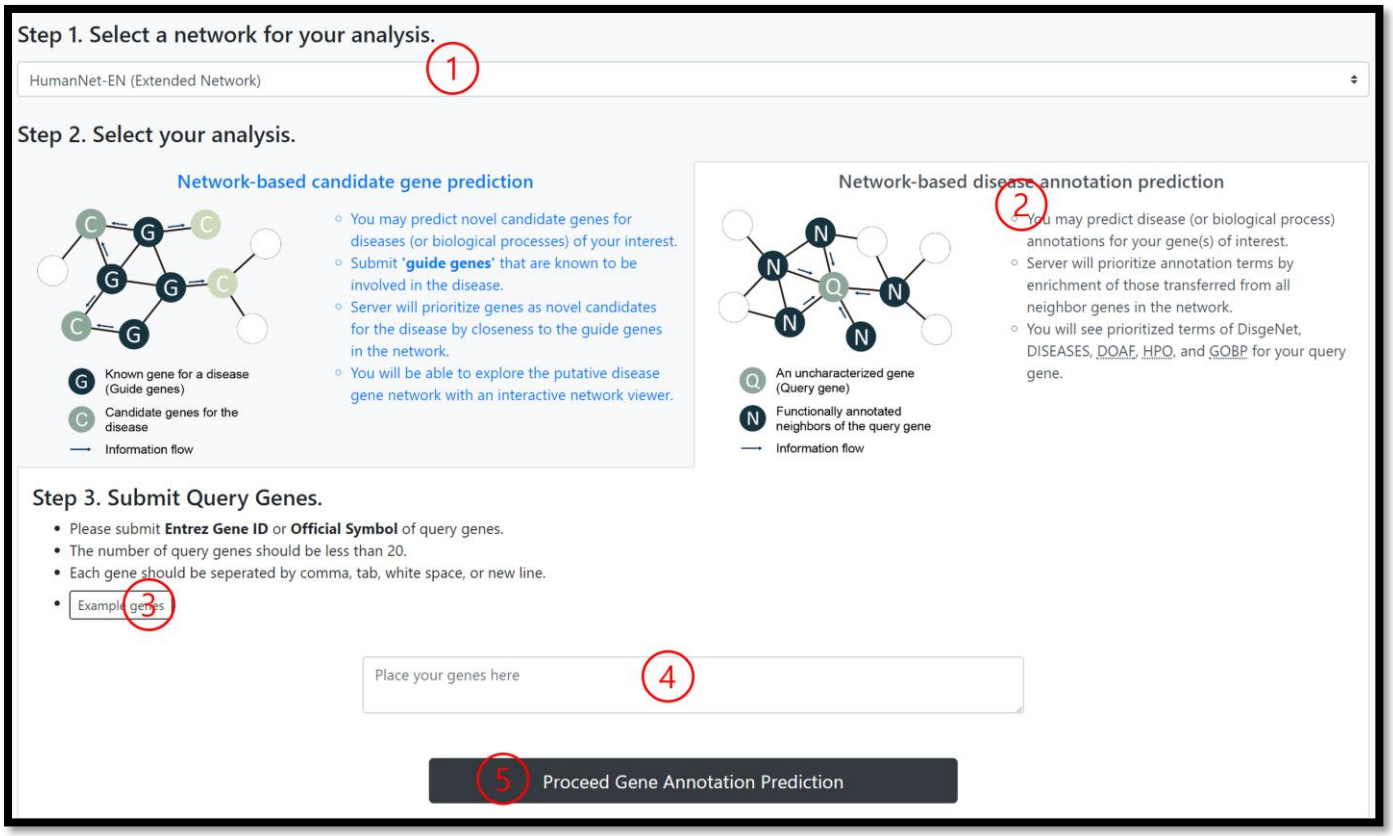
⑱ You can highlight the gene or find more information of the gene.

-  : You can highlight the gene.
-  : You can find more information about the gene on genecards.org

2. Network-based disease annotation prediction.

If you want to identify new disease (or biological process) annotations for a gene of your interest, it can be predicted by functionally annotated network neighborhoods. In the HumanNet, genes are connected when they have a high probability of having a common disease. Disease annotation prediction analysis gathers disease annotations (DisGeNET, DISEASES, DOAF, HPO, and GOBP) from the neighboring genes and prioritizes candidate disease annotations by its significance.

2-1. Gene submission form



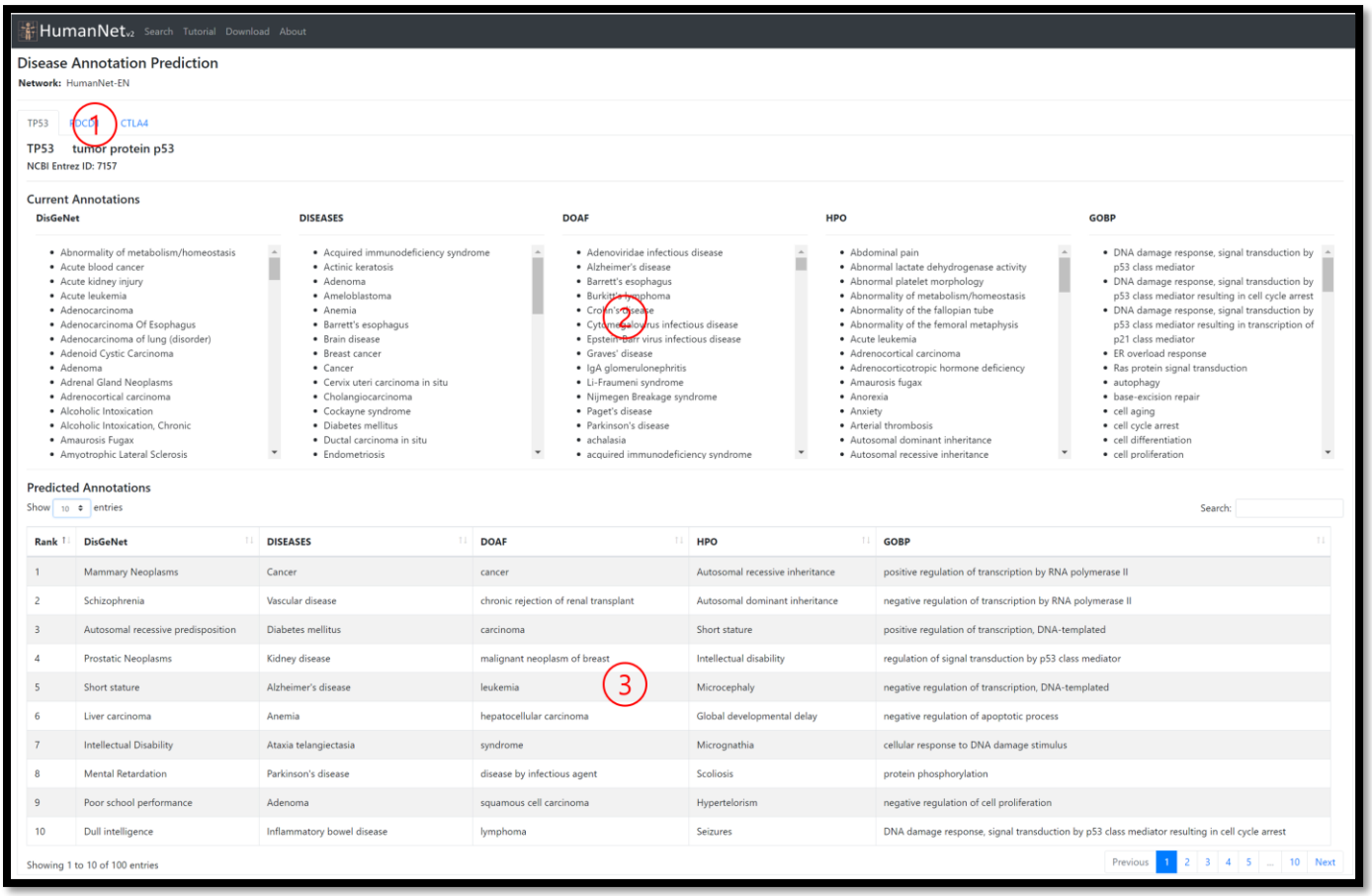
① Select a network for your analysis.

② Click "Network-based disease annotation prediction" for disease annotation prediction.

③ Submit your query genes here.

- Please submit Entrez Gene ID or Official Symbol of query genes.
- The number of query genes should be less than 20.
- Each gene should be separated by comma, tab, white space, or new line.
- If you submit multiple genes, each gene will be calculated independently.

2-2. Disease annotation prediction result.

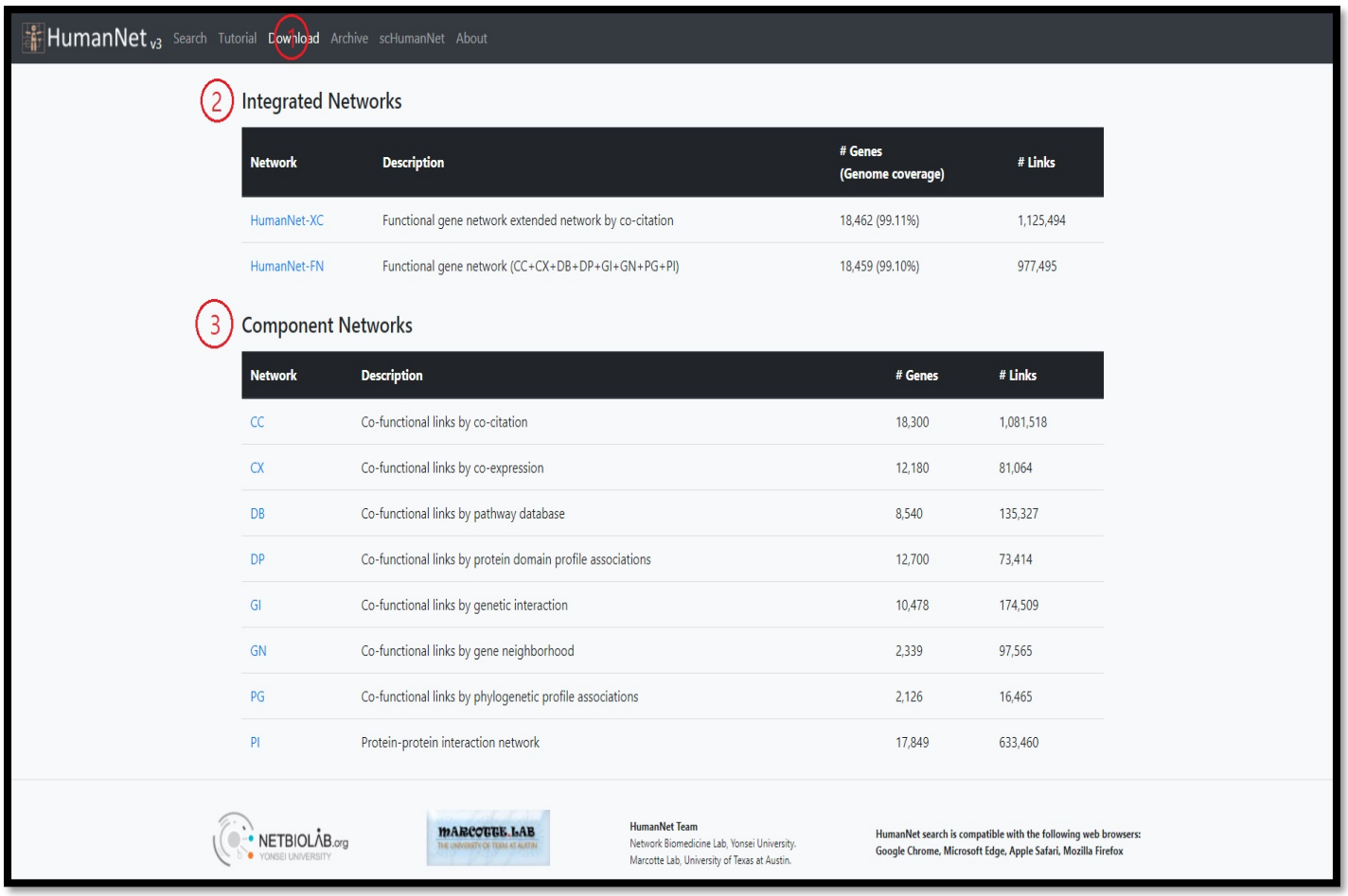


① If you submit multiple genes, you can select a gene in this tab.

② You can find the disease annotations of query gene.

③ You can examine the disease annotation of query genes predicted by the HumanNet. The disease terms are sorted by its significance of association.

3. Network download.



① You can download the HumanNet and its component networks on the Download tab.

② You can download Integrated HumanNet. Click to download the network.

③ You can also download all the component networks of the HumanNet. Click to download the network.