

# HumanNet v3 Tutorial

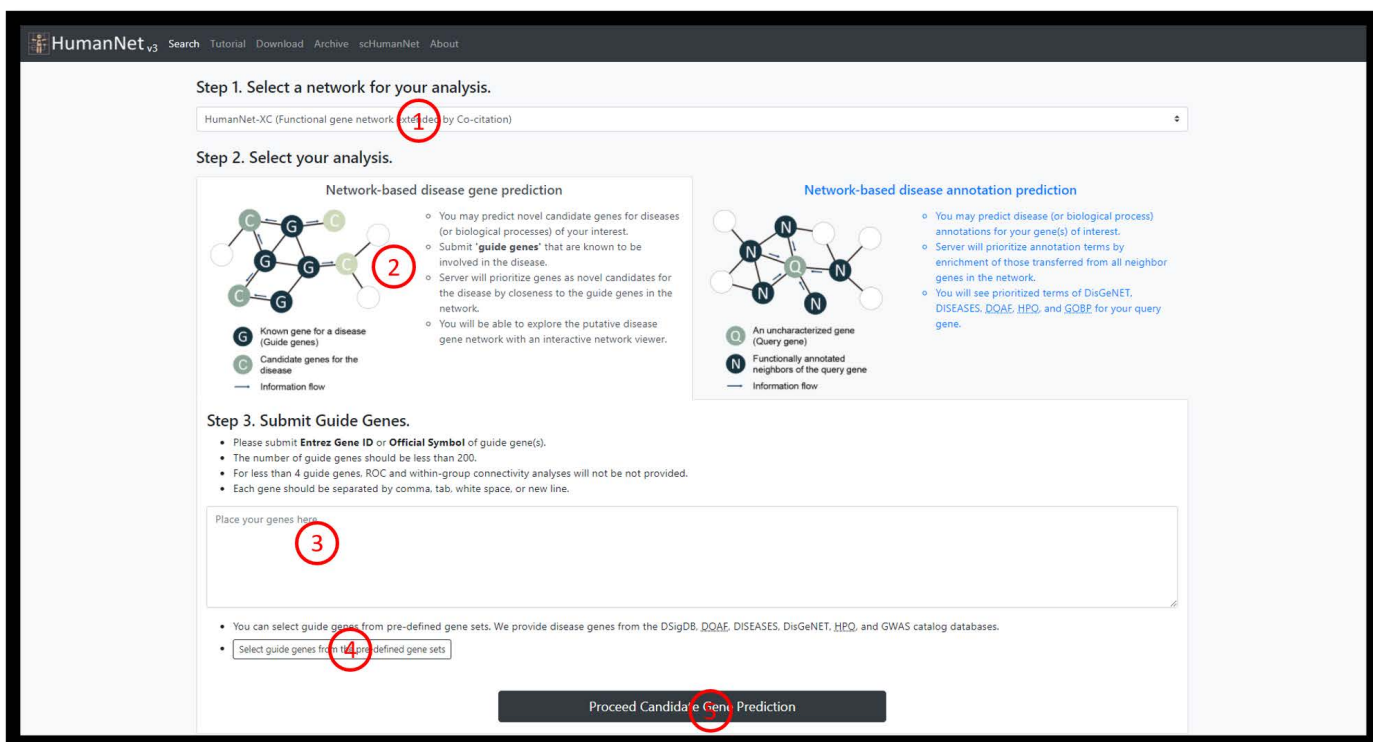
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# 1. Network-based candidate gene prediction.

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)

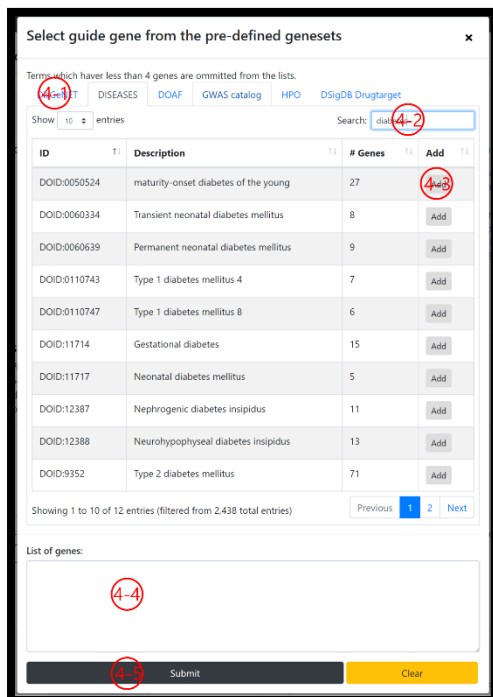
- **PI** Protein-protein interaction network

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 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

The screenshot displays a candidate gene prediction interface with several key components:



- Network View (1):** A central network diagram with TGFBI as the hub gene, connected to various other genes like PRKCSH, TNF, IL5, CXCL8, CD40LG, IL4, COL2A1, NODAL, FLNA, and NKX2-5. A search bar (3) is located at the top right of the network.
- Score Threshold (4):** A slider set to 8.30.
- Current Selection (6-1):** A panel showing details for TGFBI, including its official symbol, Entrez Gene ID (1046), full name (transforming growth factor beta 1), and score (14.6792). It also lists evidences (DB, CX, DP, LC) and annotations (DISEASES).
- Current Selection (6-2):** A panel showing details for BRCA1, including its official symbol, Entrez Gene ID (1046), full name (breast cancer 1), and score (10.1111).
- ROC Analysis (13):** Two AUROC plots comparing guide genes and random genes. The AUROC for guide genes is 0.7116 (p-value < 0.0001), and for random genes it is 1.527e-3 (p-value < 0.0001).
- Number of Candidate Genes (12):** A histogram showing the connectivity distribution of 71 random genes.
- Number of Candidate Genes (15):** A list of 71 guide genes and 1 candidate gene that are not defined in HumanNet-XC.
- Number of Candidate Genes (17):** A table listing the top 10 candidate genes with their ranks, gene names, NCBI Gene IDs, scores, and descriptions.

Rank	Gene	NCBI GeneID	Score	Description
1	RFX6	222546	23.2759	regulatory factor X6
2	RFX4	5078	22.4710	paired box 4
2	NEUROG3	50674	22.4710	neurogenin 3
4	SLC2A2	6514	17.5395	solute carrier family 2 member 2
5	G6K	2645	15.9711	glucokinase
6	HNF1A	6927	14.4433	HNF1 homeobox A
7	PDX1	3651	10.7877	pancreatic and duodenal homeobox 1
8	HNF4A	3172	10.4433	hepatocyte nuclear factor 4 alpha
9	PCBD2	84105	7.8616	pterin-4 alpha-carboxylanine dehydratase 2
10	PCBD1	5282	7.4587	pterin-4 alpha-carboxylanine dehydratase 1

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.

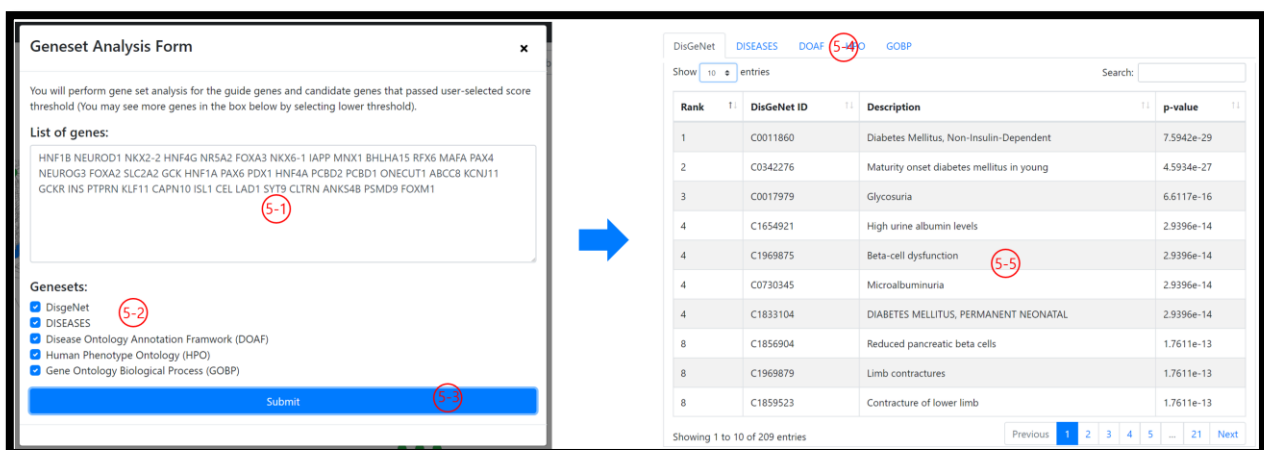
-  Move the screen.
-  Focus the network.
- Vertical bar: Zoom in or out.

## 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.



The screenshot displays the 'Geneset Analysis Form' on the left and the 'DisGeNet' results table on the right. A blue arrow points from the form to the table.

**Geneset Analysis Form:**

You will perform gene set analysis for the guide genes and candidate genes that passed user-selected score threshold (You may see more genes in the box below by selecting lower threshold).

**List of genes:**

HNF1B NEUROD1 NKX2-2 HNF4G NR5A2 FOXA3 NKX6-1 IAPP MNX1 BHLHA15 RFX6 MAFA PAX4 NEUROG3 FOXA2 SLC2A2 GSK HNF1A PAX6 PDX1 HNF4A PCBD2 PCBD1 ONECUT1 ABCC8 KCNU11 GSKR INS PTPRN KLF11 CAPN10 ISL1 CEL LAD1 SYT9 CLTRN ANKS4B PSM09 FOXM1 (5-1)

**Genesets:**

- DisGeNet (5-2)
- DISEASES
- Disease Ontology Annotation Framework (DOAF)
- Human Phenotype Ontology (HPO)
- Gene Ontology Biological Process (GOBP)

**DisGeNet Results Table:**

Rank	DisGeNet ID	Description	p-value
1	C0011860	Diabetes Mellitus, Non-Insulin-Dependent	7.5942e-29
2	C0342276	Maturity onset diabetes mellitus in young	4.5934e-27
3	C0017979	Glycosuria	6.6117e-16
4	C1654921	High urine albumin levels	2.9396e-14
4	C1969875	Beta-cell dysfunction (5-3)	2.9396e-14
4	C0730345	Microalbuminuria	2.9396e-14
4	C1833104	DIABETES MELLITUS, PERMANENT NEONATAL	2.9396e-14
8	C1856904	Reduced pancreatic beta cells	1.7611e-13
8	C1969879	Limb contractures	1.7611e-13
8	C1859523	Contracture of lower limb	1.7611e-13

Showing 1 to 10 of 209 entries

(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](https://www.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

The screenshot displays the HumanNet-EN interface for disease annotation prediction. It is divided into three main steps:

- Step 1. Select a network for your analysis.** A dropdown menu is set to "HumanNet-EN (Extended Network)".
- Step 2. Select your analysis.** Two options are presented:
  - Network-based candidate gene prediction:** Includes a diagram with green nodes (G) and white nodes (C). Legend: G = Known gene for a disease (Guide genes), C = Candidate genes for the disease, — = Information flow. Text: "You may predict novel candidate genes for diseases (or biological processes) of your interest. Submit 'guide genes' that are known to be involved in the disease. Server will prioritize genes as novel candidates for the disease by closeness to the guide genes in the network. You will be able to explore the putative disease gene network with an interactive network viewer."
  - Network-based disease annotation prediction:** Includes a diagram with a central green node (Q) and surrounding black nodes (N). Legend: Q = An uncharacterized gene (Query gene), N = Functionally annotated neighbors of the query gene, — = Information flow. Text: "You may predict disease (or biological process) annotations for your gene(s) of interest. Server will prioritize annotation terms by enrichment of those transferred from all neighbor genes in the network. You will see prioritized terms of DisGeNET, DISEASES, DOAF, HPO, and GOBP for your query gene."
- Step 3. Submit Query Genes.** Includes instructions: "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." Below this is a text input field labeled "Place your genes here" and a "Proceed Gene Annotation Prediction" button.

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.

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### Disease Annotation Prediction

Network: HumanNet-EN

TP53 **CDCC1** CTLA4

TP53 tumor protein p53  
NCBI Entrez ID: 7157

#### Current Annotations

DisGeNet	DISEASES	DOAF	HPO	GOBP
<ul style="list-style-type: none"> <li>Abnormality of metabolism/homeostasis</li> <li>Acute blood cancer</li> <li>Acute kidney injury</li> <li>Acute leukemia</li> <li>Adenocarcinoma</li> <li>Adenocarcinoma Of Esophagus</li> <li>Adenocarcinoma of lung (disorder)</li> <li>Adenoid Cystic Carcinoma</li> <li>Adenoma</li> <li>Adrenal Gland Neoplasms</li> <li>Adrenocortical carcinoma</li> <li>Alcoholic Intoxication</li> <li>Alcoholic Intoxication, Chronic</li> <li>Amaurosis Fugax</li> <li>Amotrophic Lateral Sclerosis</li> </ul>	<ul style="list-style-type: none"> <li>Acquired immunodeficiency syndrome</li> <li>Actinic keratosis</li> <li>Adenoma</li> <li>Ameloblastoma</li> <li>Anemia</li> <li>Barrett's esophagus</li> <li>Brain disease</li> <li>Breast cancer</li> <li>Cancer</li> <li>Cervix uteri carcinoma in situ</li> <li>Cholangiocarcinoma</li> <li>Cockayne syndrome</li> <li>Diabetes mellitus</li> <li>Ductal carcinoma in situ</li> <li>Endometriosis</li> </ul>	<ul style="list-style-type: none"> <li>Adenoviridae infectious disease</li> <li>Alzheimer's disease</li> <li>Barrett's esophagus</li> <li>Burkitt's lymphoma</li> <li>Crohn's disease</li> <li>Cytomegalovirus infectious disease</li> <li>Epstein-Barr virus infectious disease</li> <li>Graves' disease</li> <li>IgA glomerulonephritis</li> <li>Li-Fraumeni syndrome</li> <li>Nijmegen Breakage syndrome</li> <li>Paget's disease</li> <li>Parkinson's disease</li> <li>achalasia</li> <li>acquired immunodeficiency syndrome</li> </ul>	<ul style="list-style-type: none"> <li>Abdominal pain</li> <li>Abnormal lactate dehydrogenase activity</li> <li>Abnormal platelet morphology</li> <li>Abnormality of metabolism/homeostasis</li> <li>Abnormality of the fallopian tube</li> <li>Abnormality of the femoral metaphysis</li> <li>Acute leukemia</li> <li>Adrenocortical carcinoma</li> <li>Adrenocorticotrophic hormone deficiency</li> <li>Amaurosis fugax</li> <li>Anorexia</li> <li>Anxiety</li> <li>Arterial thrombosis</li> <li>Autosomal dominant inheritance</li> <li>Autosomal recessive inheritance</li> </ul>	<ul style="list-style-type: none"> <li>DNA damage response, signal transduction by p53 class mediator</li> <li>DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest</li> <li>DNA damage response, signal transduction by p53 class mediator resulting in transcription of p21 class mediator</li> <li>ER overload response</li> <li>Ras protein signal transduction</li> <li>autophagy</li> <li>base-excision repair</li> <li>cell aging</li> <li>cell cycle arrest</li> <li>cell differentiation</li> <li>cell proliferation</li> </ul>

#### Predicted Annotations

Show 10 entries

Rank	DisGeNet	DISEASES	DOAF	HPO	GOBP
1	Mammary Neoplasms	Cancer	cancer	Autosomal recessive inheritance	positive regulation of transcription by RNA polymerase II
2	Schizophrenia	Vascular disease	chronic rejection of renal transplant	Autosomal dominant inheritance	negative regulation of transcription by RNA polymerase II
3	Autosomal recessive predisposition	Diabetes mellitus	carcinoma	Short stature	positive regulation of transcription, DNA-templated
4	Prostatic Neoplasms	Kidney disease	malignant neoplasm of breast	Intellectual disability	regulation of signal transduction by p53 class mediator
5	Short stature	Alzheimer's disease	leukemia	Microcephaly	negative regulation of transcription, DNA-templated
6	Liver carcinoma	Anemia	hepatocellular carcinoma	Global developmental delay	negative regulation of apoptotic process
7	Intellectual Disability	Ataxia telangiectasia	syndrome	Micrognathia	cellular response to DNA damage stimulus
8	Mental Retardation	Parkinson's disease	disease by infectious agent	Scoliosis	protein phosphorylation
9	Poor school performance	Adenoma	squamous cell carcinoma	Hypertelorism	negative regulation of cell proliferation
10	Dull intelligence	Inflammatory bowel disease	lymphoma	Seizures	DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest

Showing 1 to 10 of 100 entries

Previous 1 2 3 4 5 ... 10 Next

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.

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#### ② Integrated Networks

Network	Description	# Genes (Genome coverage)	# Links
<a href="#">HumanNet-XC</a>	Functional gene network extended network by co-citation	18,462 (99.11%)	1,125,494
<a href="#">HumanNet-FN</a>	Functional gene network (CC+CX+DB+DP+GI+GN+PG+PI)	18,459 (99.10%)	977,495

#### ③ Component Networks

Network	Description	# Genes	# Links
<a href="#">CC</a>	Co-functional links by co-citation	18,300	1,081,518
<a href="#">CX</a>	Co-functional links by co-expression	12,180	81,064
<a href="#">DB</a>	Co-functional links by pathway database	8,540	135,327
<a href="#">DP</a>	Co-functional links by protein domain profile associations	12,700	73,414
<a href="#">GI</a>	Co-functional links by genetic interaction	10,478	174,509
<a href="#">GN</a>	Co-functional links by gene neighborhood	2,339	97,565
<a href="#">PG</a>	Co-functional links by phylogenetic profile associations	2,126	16,465
<a href="#">PI</a>	Protein-protein interaction network	17,849	633,460

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HumanNet search is compatible with the following web browsers:  
Google Chrome, Microsoft Edge, Apple Safari, Mozilla Firefox

- 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.