

Supplement 4

Analysis Supplement – Visualization of the Receptor Interactome

As described in the main text and Supplement S2, the receptor interactome includes interactions for each human membrane receptor in the HPMR database [1]. Totally, there are 904 receptor genes and for each one of them, we identified their potential protein binding partners from all possible 24380 human genes based on their listing in the NCBI database. The thresholded graph contains ~9100 edges, which relates to 559 membrane receptors and 1750 non-receptors. Interactions between non-receptor genes are not evaluated and considered in this graph. Visualizations of this graph and selected sub networks are shown here.

1. About the visualization

Visualizations were done by using Cytoscape software [3]. Selected sub networks are shown in both predicted receptor interactome and the mapped subgraphs in HPRD [2]. The nodes are labeled with different colors. Green corresponds to type I receptors and blue represents GPCRs. Genes not in HPMR [1] are considered as non-receptors and are shown as red nodes, except when distinguishing ligands from non-ligands. Pink color is used for highlighting ligands where indicated.

Ligands were extracted based on the Gene Ontology [4]. We first filtered the GO terms involving “ligands” and manually verified the resulting list. Using these GO-ligand terms, we then filtered the human gene list and found 697 ligand genes.

For all visualizations below, we show the graphs derived from our predicted receptor interactome and the corresponding graph created based on the retrieval of the respective known interactions from HPRD [2].

2. Number of nodes or edges in selected sub graphs of the receptor interactome

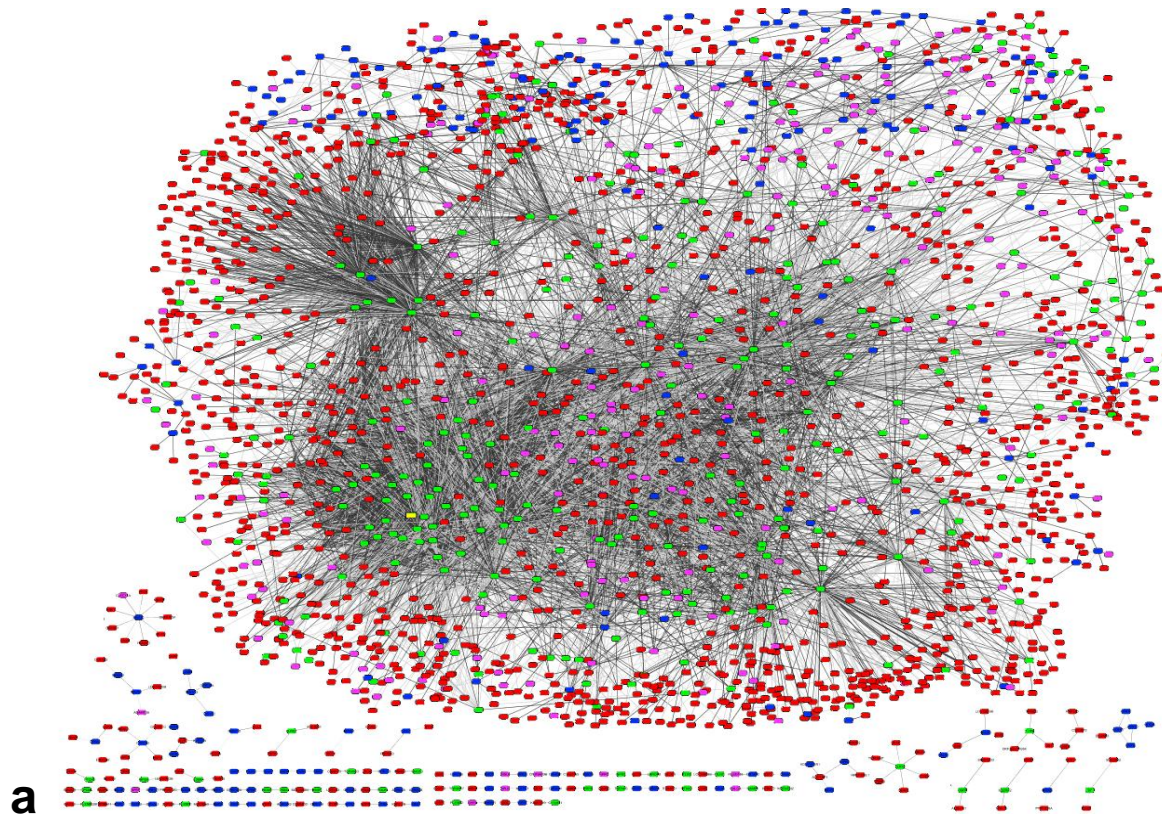
In 0, we list the basic statistics of selected graphs visualized. This information includes the number of edges, the number of nodes having partners, the number of GPCR proteins this graph has, and the number of type I receptors. If applicable, the number of ligand gene nodes in the graph are indicated.

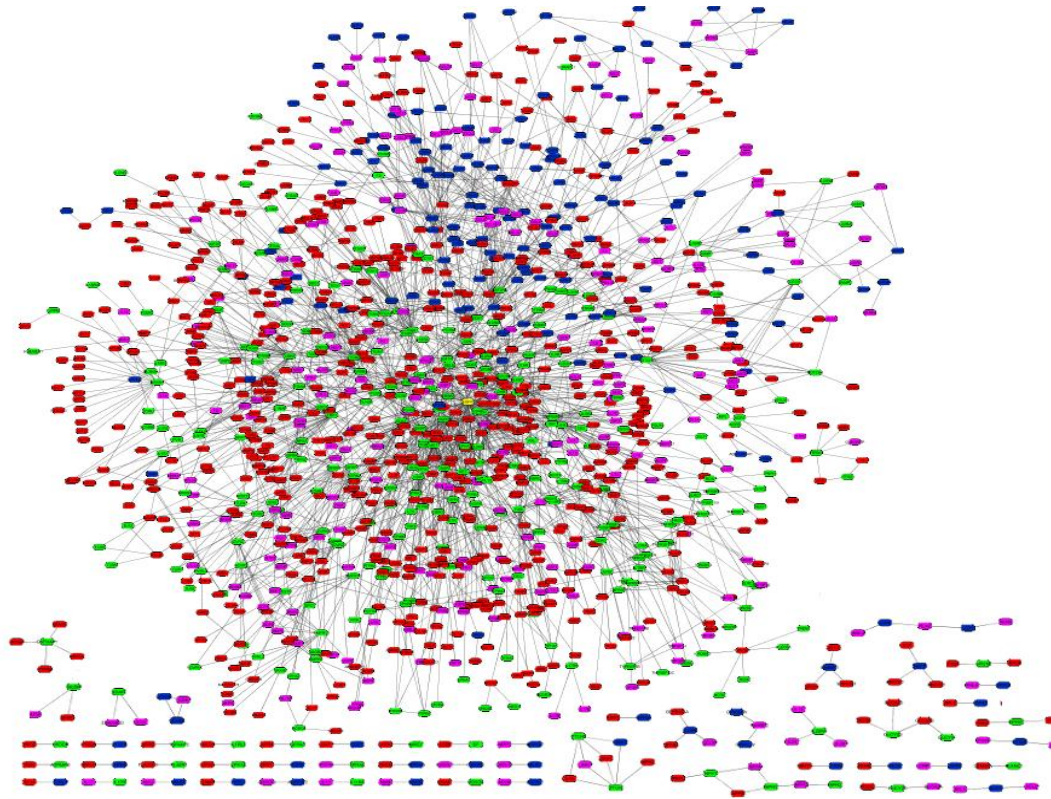
Table S4.1 The node composition of selected subgraphs in the receptor interactome. The score threshold was 2.0.

Graph	Total Nodes (Degree>0)	Total Edge	GPCR node (GREEN)	Type I node (BLUE)	Ligands Node (PINK)
Predicted receptor interactome	2309	9144	236	323	249
Predicted Receptor-Receptor	356	1775	121	235	0
Predicted Receptor-Ligands	525	1363	76	201	248
Predicted EGFR-subgraph	148	1720	0	46	21
HPRD receptor interactome	1455	2522	294	181	273
HPRD Receptor-Receptor	168	171	37	131	0
HPRD Receptor-Ligands	550	688	192	85	273
HPRD EGFR-subgraph	92	135	0	7	14

3. Visualization of the receptor interactome – predicted and known

Shown in Fig. S4.1a below is the full receptor graph generated with a score cutoff of 2.0. It contains 2309 unique genes having partners, with 236 among them are GPCRs and 323 of them are type I receptors. Nodes are connected by 9144 edges. A reduced version of this graph is also presented in Fig. 1b of the main text, where groups of small connected components (totally 205 nodes and 131 edges) were omitted. All receptors related interaction pairs in HPRD are visualized in Fig. S4.1b. This network contains 1455 genes with degree larger than 0 and 2522 edges among them.





b

Figure S4.1 Visualization of the entire receptor interactome. Blue represents GPCR's, green represents type I receptors, except EGFR, which is labeled as a yellow node. Pink color is used for the ligands. Other human gene nodes are shown in red. (a). The whole predicted receptor interactome contains 2309 nodes and 9144 edges. (b). The receptor interactome in HPRD contains 1455 nodes and 2522 edges.

4. The subgraphs related to receptors and ligands – predicted and known

Shown below are subgraphs related to receptor to receptor and receptor to ligand interactions. Here we present the entire graphs and also show their comparison with the known interactions retrieved from the HPRD. In Fig. S4.4 we superimpose Fig. S4.2 and Fig. S4.3 to show all nodes and edges connecting receptors and ligands with themselves and with each other.

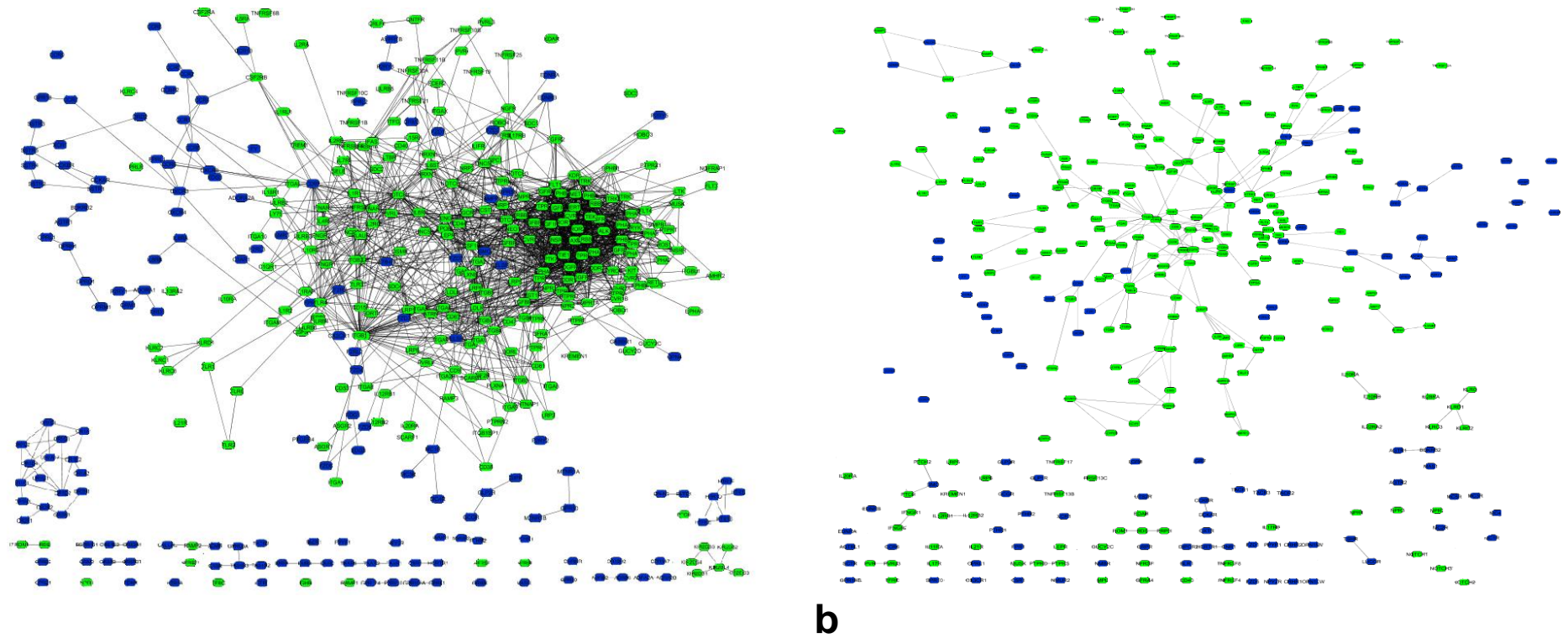
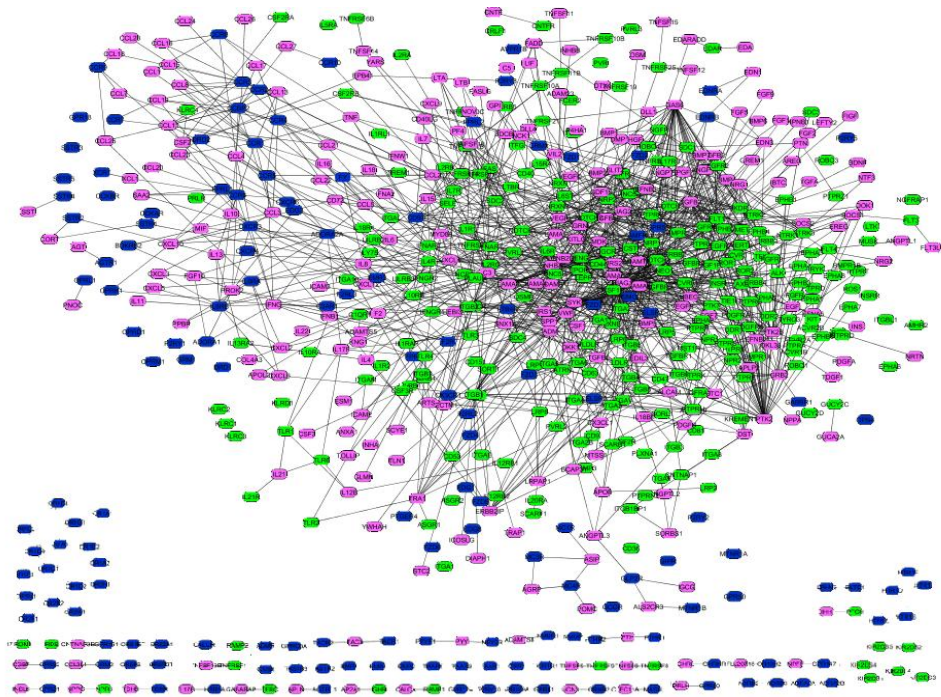
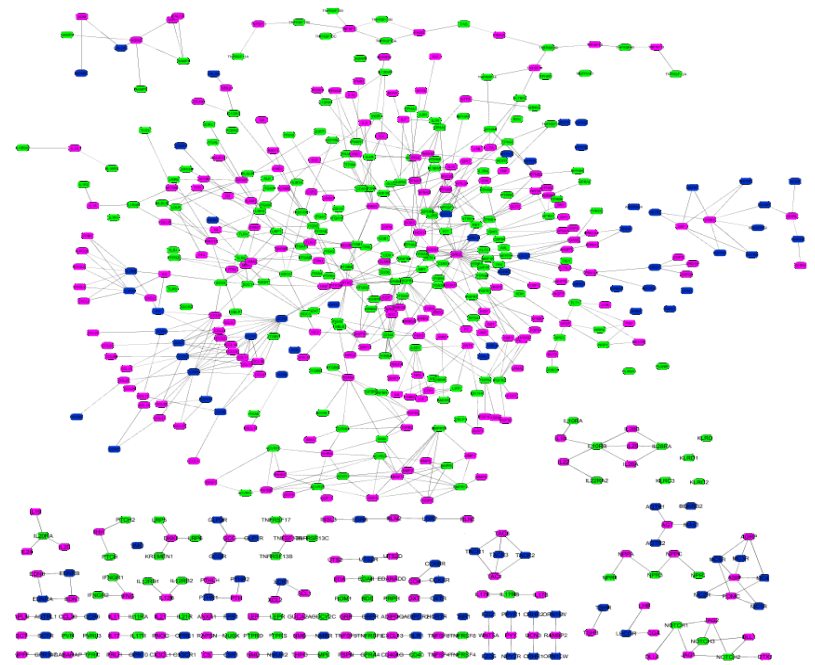


Figure S4.2 The receptor to receptor subgraph. Green refers to type I receptors and blue represents GPCRs. (a). Our predicted receptor interactome has 1775 edges. (b). The HPRD receptor interactome has only 171 edges.

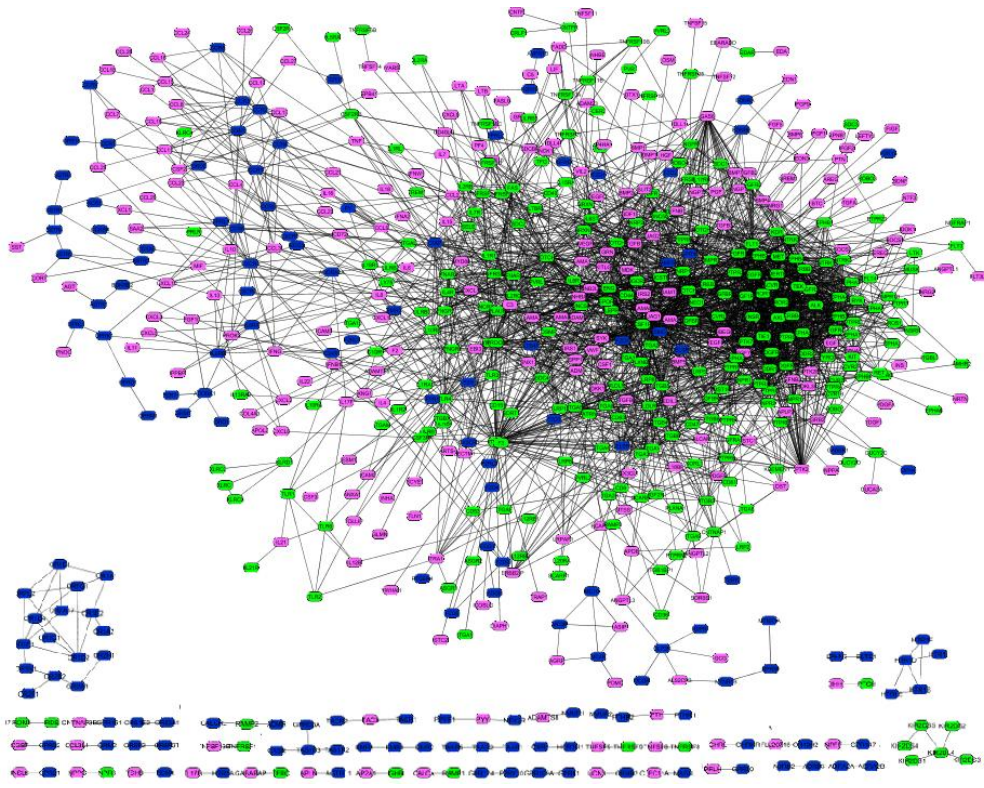


a

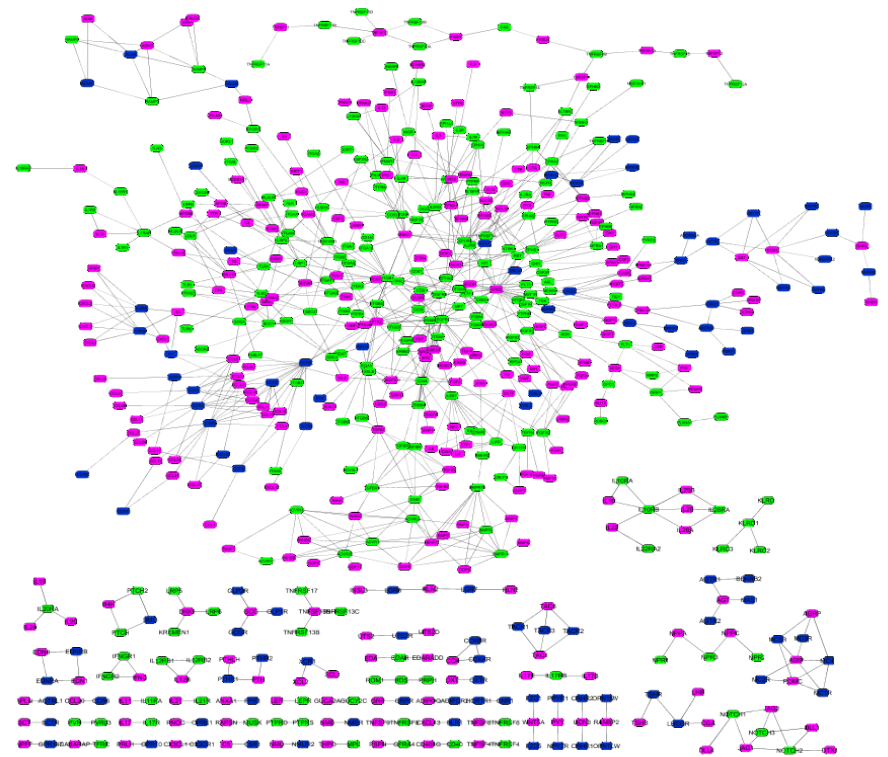


b

Figure S4.3 The receptor to ligand subgraph: Green refers to type I receptors and blue represents GPCRs. Pink color is used for the ligands. Other human gene nodes are red. (a). Our predicted receptor interactome has 1363 edges. (b). The HPRD receptor interactome has 688 edges.



a



b

Figure S4.4 Subgraph containing all receptors and ligands. Green refers to type I receptors and blue represents GPCRs. Pink color is used for the ligands. Other human gene nodes are red. (a). Our predicted receptor interactome has 664 nodes and 3138 edges. (b). The HPRD receptor interactome has 604 nodes and 859 edges.

5. The subgraphs connected to EGFR – predicted and known

The subgraphs shown in Fig. S4.5 are connected to the EGFR. These subgraphs contain all the interaction partners of the EGFR and all the edges between them in the receptor interactome. We find no GPCR partners in both predicted and HPRD graphs for the EGFR.

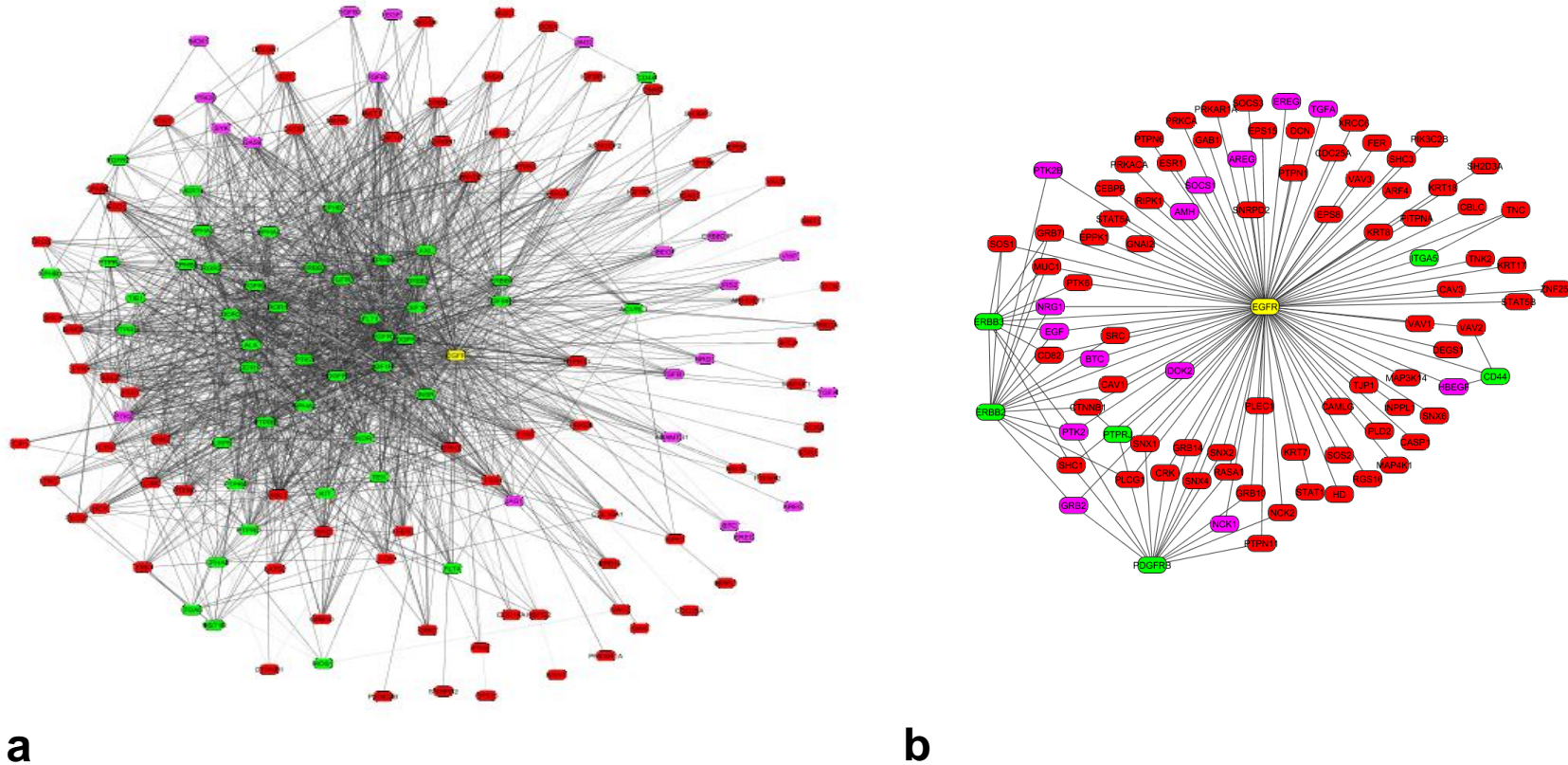


Figure S4.5 EGFR related subgraphs. Green refers to type I receptors and blue represents GPCRs, except that EGFR is labeled as a yellow node. Pink color is used for the ligands. Other human gene nodes are red. (a). Our predicted receptor interactome has 148 nodes and 1720 edges. (b). The HPRD receptor interactome has 92 nodes and 135 edges.

Bibliography

1. Ben-Shlomo I, Yu Hsu S, Rauch R, Kowalski HW, Hsueh AJ., Signaling receptome: a genomic and evolutionary perspective of plasma membrane receptors involved in signal transduction. *Sci STKE*. 2003. 187: RE9
2. Mishra GR, Suresh M, Kumaran K, Kannabiran N, et al. and Pandey A. Human protein reference database--2006 update. *Nucleic Acids Res* 2006 Jan 1; 34(Database issue) D411-4.
3. Cytoscape, www.cytoscape.org (2006)
4. The Gene Ontology Consortium, Gene Ontology: tool for the unification of biology. *Nature Genet*. 2000; 25 25-29.