

Supplementary Information

Fig. S1. Comparing the connectivity matrix obtained by the RWR method to those by a method based on the hyper-geometric distribution. The method based on the hyper-geometric distribution (HGD) directly utilizes shared domain annotations to build the connectivity matrix. **(A)** Venn diagram illustrating the differences and intersections of interconnections identified by both methods. **(B)** Boxplot illustrating the distribution of FDR values grouped according to the venn diagram in A. Left panel: the distribution of FDR values resulting from the RWR method. Right panel: the distribution of FDR values resulting from the HGD method. RWR+ (HGD+) is used for indicating all interconnections identified by the RWR method (or the HGD method); RWR+HGD+ for common interconnections identified by both methods; RWR+HGD- (or RWR-HGD+) for unique interconnections identified only by the RWR method (or the HGD method).

Fig. S2. Comparing the connectivity matrix resulting from the RWR method and a method using direct neighbor information. The method using direct neighbor information (DNI) relies on the interacting information in the input network to infer the connectivity matrix. **(A)** Venn diagram illustrating the differences and intersections of interconnections identified by both methods. **(B)** Boxplot illustrating the distribution of FDR values grouped according to the venn diagram in A. Left panel: the distribution of FDR values obtained from the RWR method. Right panel: the distribution of FDR values obtained from the DNI method. RWR+ (DNI+) is used for indicating all interconnections identified by the RWR method (or the DNI method); RWR+DNI+ for common interconnections identified by both methods; RWR+DNI- (or RWR-DNI+) for unique interconnections identified only by the RWR method (or the DNI method).

Fig. S3. The connectivity matrix for below-average AUC terms. The matrix is colour-encoded according to connectivity scores, and is also marked with the statistically significant connections.

Table S1. The prediction of the top 25 drug-disease connections by RWR.

Table S2. The RWR-based prediction of the top 25 disease-phenotype connections in human.

Table S3. The prediction of the top 25 cross-species phenotype connections by RWR.

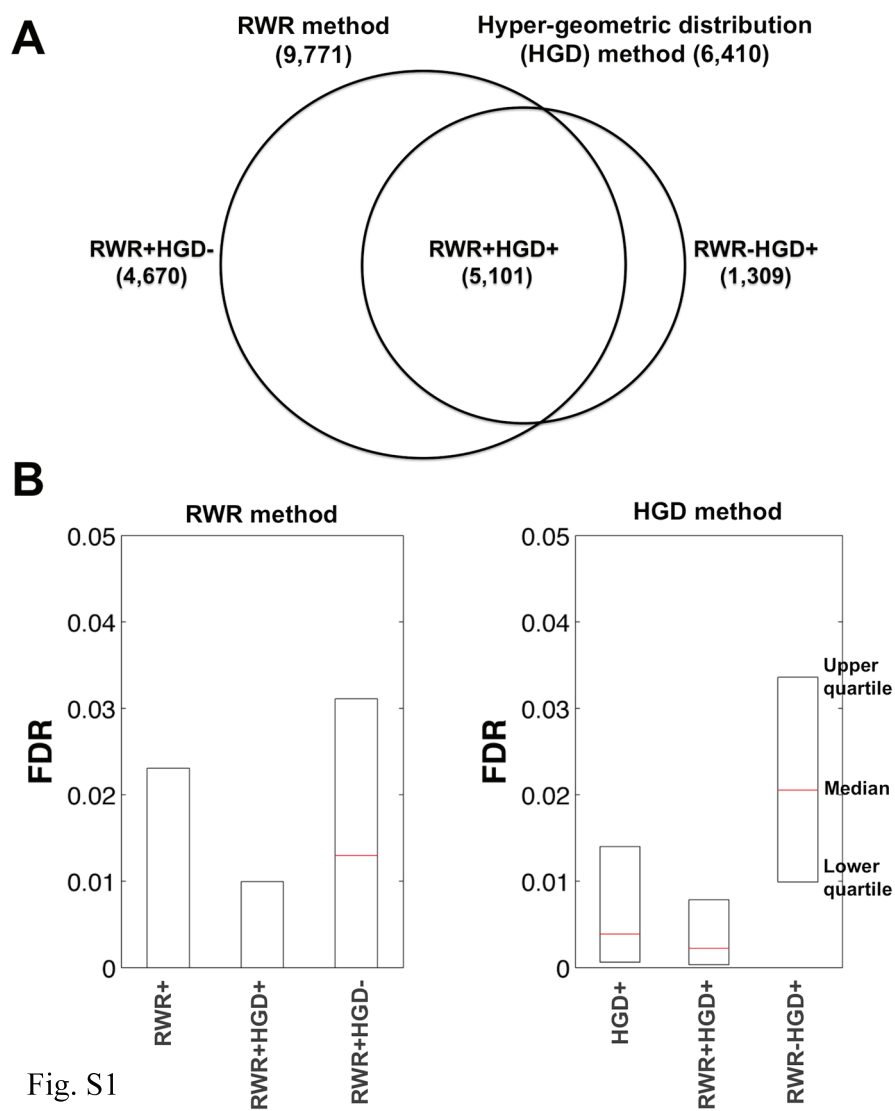


Fig. S1

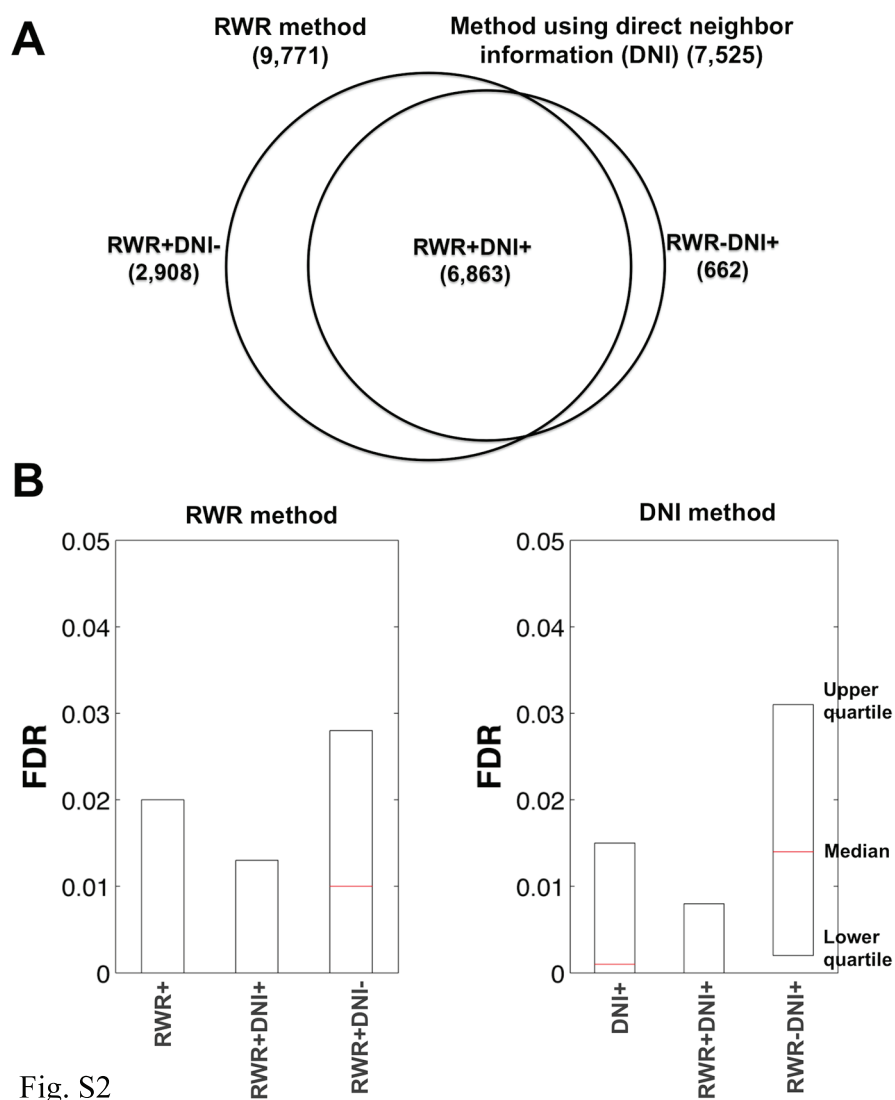


Fig. S2

Table S1. The prediction of the top 25 drug-disease connections by RWR

Top* (Rank)	DrugBank ATC code		Disease Ontology		Statistical Significance		Common Connections**	
	ID	Name	ID	Name	C-score	FDR	HGD	DNI
1	B01AC	platelet aggregation inhibitors excl. heparin	DOID:936	brain disease	14.75	0.00E+00	1	1
2	B01AC	platelet aggregation inhibitors excl. heparin	DOID:331	central nervous system disease	10.41	0.00E+00	1	1
3	R01AX	other nasal preparations	DOID:936	brain disease	9.91	0.00E+00	0	1
4	S01AX	other antiinfectives	DOID:936	brain disease	8.82	0.00E+00	0	0
5	A11HA03	tocopherol (vitamin E)	DOID:3118	hepatobiliary disease	8.04	1.47E-02	0	0
6	B01AC	platelet aggregation inhibitors excl. heparin	DOID:50	thyroid gland disease	7.53	3.65E-02	0	0
7	R01AX	other nasal preparations	DOID:331	central nervous system disease	6.62	0.00E+00	0	0
8	S01AX	other antiinfectives	DOID:331	central nervous system disease	6.56	2.52E-03	0	1
9	A01AB	antiinfectives and antiseptics for local oral treatment	DOID:936	brain disease	6.41	0.00E+00	0	1
10	D10AD	retinoids for topical use in acne	DOID:10283	prostate cancer	6.26	4.23E-02	0	0
11	D10AD	retinoids for topical use in acne	DOID:3856	male reproductive organ cancer	6.26	4.23E-02	0	1
12	V03AF	detoxifying agents for antineoplastic treatment	DOID:936	brain disease	6.12	2.22E-03	0	1
13	V03AB	antidotes	DOID:936	brain disease	5.89	0.00E+00	1	1
14	V03AB	antidotes	DOID:331	central nervous system disease	5.89	0.00E+00	1	1
15	D10AD	retinoids for topical use in acne	DOID:120	female reproductive organ cancer	5.87	1.32E-02	0	1
16	D10AD	retinoids for topical use in acne	DOID:37	skin disease	5.75	3.09E-02	0	0
17	D10AD	retinoids for topical use in acne	DOID:193	reproductive organ cancer	5.36	1.32E-02	0	0
18	V03AB	antidotes	DOID:3118	hepatobiliary disease	5.27	3.99E-02	0	0
19	S02AA	antiinfectives	DOID:936	brain disease	5.09	3.50E-02	0	0
20	A11HA03	tocopherol (vitamin E)	DOID:1240	leukemia	4.400	4.83E-02	0	0
21	A09AB	acid preparations	DOID:331	central nervous system disease	4.39	5.67E-03	0	1
22	G01AF	imidazole derivatives	DOID:331	central nervous system disease	4.29	2.52E-03	0	1
23	D10AD	retinoids for topical use in acne	DOID:3118	hepatobiliary disease	4.18	4.21E-02	0	0
24	A11HA	other plain vitamin preparations	DOID:331	central nervous system disease	4.07	2.63E-02	1	1
25	V03AF	detoxifying agents for antineoplastic treatment	DOID:331	central nervous system disease	3.96	5.67E-03	0	0

*Only consider drug groups at the 4th and 5th levels (i.e., chemical properties) according to Anatomical Therapeutic Chemical (ATC) classification system.

**The common connections identified either by the method based on hyper-geometric distribution (HGD) or by the method using direct neighbor information (DNI).

Table S2. The RWR-based prediction of the top 25 disease-phenotype connections in human

Top (Rank)	Human Phenotype		Mouse Phenotype		Statistical Significance		Common Connections**	
	ID	Name	ID	Name	C-score	FDR	HGD	DNI
1	DOID:50	thyroid gland disease	MP:0008555	abnormal interferon secretion	16.31	0.00E+00	1	1
2	DOID:50	thyroid gland disease	MP:0008559	abnormal interferon-gamma secretion	16.31	0.00E+00	1	1
3	DOID:229	female reproductive system disease	MP:0011504	abnormal limb long bone morphology	16.30	0.00E+00	0	1
4	DOID:229	female reproductive system disease	MP:0002115	abnormal limb bone morphology	16.30	0.00E+00	1	1
5	DOID:229	female reproductive system disease	MP:0002109	abnormal limb morphology	15.73	0.00E+00	0	0
6	DOID:403	mouth disease	MP:0003711	pathological neovascularization	15.34	0.00E+00	0	0
7	DOID:229	female reproductive system disease	MP:0005371	limbs/digits/tail phenotype	14.84	0.00E+00	1	1
8	DOID:1091	tooth disease	MP:0002109	abnormal limb morphology	14.60	0.00E+00	1	1
9	DOID:15	reproductive system disease	MP:0011504	abnormal limb long bone morphology	14.31	0.00E+00	1	1
10	DOID:15	reproductive system disease	MP:0002115	abnormal limb bone morphology	14.31	0.00E+00	1	1
11	DOID:403	mouth disease	MP:0002109	abnormal limb morphology	14.19	0.00E+00	1	1
12	DOID:1091	tooth disease	MP:0003711	pathological neovascularization	14.07	0.00E+00	0	1
13	DOID:1091	tooth disease	MP:0011504	abnormal limb long bone morphology	13.98	0.00E+00	0	1
14	DOID:1091	tooth disease	MP:0002115	abnormal limb bone morphology	13.98	0.00E+00	0	1
15	DOID:0050117	disease by infectious agent	MP:0000696	abnormal Peyer's patch morphology	13.97	0.00E+00	1	1
16	DOID:0050117	disease by infectious agent	MP:0002378	abnormal gut-associated lymphoid tissue morphology	13.97	0.00E+00	1	0
17	DOID:403	mouth disease	MP:0011504	abnormal limb long bone morphology	13.95	0.00E+00	1	1
18	DOID:403	mouth disease	MP:0002115	abnormal limb bone morphology	13.95	0.00E+00	1	1
19	DOID:28	endocrine system disease	MP:0008555	abnormal interferon secretion	13.89	0.00E+00	1	1
20	DOID:28	endocrine system disease	MP:0008559	abnormal interferon-gamma secretion	13.89	0.00E+00	0	1
21	DOID:229	female reproductive system disease	MP:0003723	abnormal long bone morphology	13.83	0.00E+00	1	1
22	DOID:15	reproductive system disease	MP:0002109	abnormal limb morphology	13.74	0.00E+00	1	1
23	DOID:1091	tooth disease	MP:0005371	limbs/digits/tail phenotype	13.72	0.00E+00	0	1
24	DOID:0060056	hypersensitivity reaction disease	MP:0001845	abnormal inflammatory response	13.63	0.00E+00	0	0
25	DOID:0060056	hypersensitivity reaction disease	MP:0001846	increased inflammatory response	13.62	0.00E+00	1	1

**The common connections identified either by the method based on hyper-geometric distribution (HGD) or by the method using direct neighbor information (DNI).

Table S3. The prediction of the top 25 cross-species phenotype connections by RWR

Top (Rank)	Human Phenotype		Mouse Phenotype		Statistical Significance		Common Connections**	
	ID	Name	ID	Name	C-score	FDR	HGD	DNI
1	HP:0000163	Abnormality of the oral cavity	MP:0003743	abnormal facial morphology	13.24	0.00E+00	1	1
2	HP:0000153	Abnormality of the mouth	MP:0003743	abnormal facial morphology	12.73	0.00E+00	1	1
3	HP:0100022	Abnormality of movement	MP:0005194	abnormal anterior uvea morphology	11.41	0.00E+00	1	1
4	HP:0000271	Abnormality of the face	MP:0003743	abnormal facial morphology	11.30	0.00E+00	1	1
5	HP:0100022	Abnormality of movement	MP:0001340	abnormal eyelid morphology	11.00	0.00E+00	1	1
6	HP:0100022	Abnormality of movement	MP:0001756	abnormal urination	10.95	0.00E+00	1	1
7	HP:0002795	Functional respiratory abnormality	MP:0002572	abnormal emotion/affect behavior	10.91	0.00E+00	1	1
8	HP:0000163	Abnormality of the oral cavity	MP:0000432	abnormal head morphology	10.84	0.00E+00	1	1
9	HP:0001626	Abnormality of the cardiovascular system	MP:0003878	abnormal ear physiology	10.69	0.00E+00	1	1
10	HP:0000234	Abnormality of the head	MP:0000432	abnormal head morphology	10.64	0.00E+00	1	1
11	HP:0000153	Abnormality of the mouth	MP:0000432	abnormal head morphology	10.63	0.00E+00	1	1
12	HP:0002795	Functional respiratory abnormality	MP:0009745	abnormal behavioral response to xenobiotic	10.62	0.00E+00	1	1
13	HP:0001760	Abnormality of the foot	MP:0002110	abnormal digit morphology	10.60	0.00E+00	1	1
14	HP:0001760	Abnormality of the foot	MP:0000572	abnormal autopod morphology	10.60	0.00E+00	1	1
15	HP:0000234	Abnormality of the head	MP:0003743	abnormal facial morphology	10.52	0.00E+00	0	1
16	HP:0002715	Abnormality of the immune system	MP:0005000	abnormal immune tolerance	10.51	0.00E+00	0	0
17	HP:0002715	Abnormality of the immune system	MP:0005005	abnormal self tolerance	10.51	0.00E+00	1	1
18	HP:0002715	Abnormality of the immune system	MP:0001844	autoimmune response	10.51	0.00E+00	1	1
19	HP:0000271	Abnormality of the face	MP:0005371	limbs/digits/tail phenotype	10.46	0.00E+00	1	1
20	HP:0010987	Abnormality of cellular immune system	MP:0000701	abnormal lymph node size	10.28	0.00E+00	1	1
21	HP:0000152	Abnormality of head and neck	MP:0000432	abnormal head morphology	10.26	0.00E+00	0	1
22	HP:0000234	Abnormality of the head	MP:0005371	limbs/digits/tail phenotype	10.26	0.00E+00	1	1
23	HP:0002795	Functional respiratory abnormality	MP:0001340	abnormal eyelid morphology	10.18	0.00E+00	1	0
24	HP:0100022	Abnormality of movement	MP:0003878	abnormal ear physiology	10.17	0.00E+00	1	1
25	HP:0001881	Abnormality of leukocytes	MP:0000689	abnormal spleen morphology	10.15	0.00E+00	1	1

**The common connections identified either by the method based on hyper-geometric distribution (HGD) or by the method using direct neighbor information (DNI).