Supplementary Materials:

Deciphering deterioration mechanisms of complex diseases based on the construction of dynamic networks and systems analysis

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Supplementary Text:

1. Calculation of average absolute and relative errors

In the present study, we defined two types of errors: average absolute error (AAE) and average relative error (ARE), measuring how close predictions were to the experimental data, namely the accuracy of the constructed dynamic networks. Because the absolute error relates to the dimension, it is generally a reference value. The relative error is not related to the dimension, therefore, it can reflect the difference between simulations and experimental data. In scientific computing, the relative error between the simulations and real data is an important index to prove the effectiveness of the method. The absolute error is the magnitude of the difference between the experimental value and the simulation value, and the relative error is the absolute error divided by the magnitude of the experimental value. Accordingly, AAE and ARE can be defined as follows:

$$AAE = \frac{1}{n}\sum_{i=1}^{n}\frac{1}{m}\sum_{j=1}^{m}\left|X_{ij}^{\exp}(t_r+\Delta t) - X_{ij}^{sim}(t_r+\Delta t)\right|. \tag{1}$$

$$ARE = \frac{1}{n}\sum_{i=1}^{n}\frac{1}{m}\sum_{j=1}^{m}\frac{\left|X_{ij}^{\exp}(t_r+\Delta t) - X_{ij}^{sim}(t_r+\Delta t)\right|}{\left|X_{ij}^{\exp}(t_r+\Delta t)\right|}. \tag{2}$$

In the equations (1) and (2), $X_{ij}^{sim}(t_r+\Delta t)$ and $X_{ij}^{\exp}(t_r+\Delta t)$ are the simulation value and experimental value of the *i-th* protein at time point $t_r+\Delta t$ in the *j-th* sample, respectively. $X_{ij}^{sim}(t_r+\Delta t)$ is calculated according to the following formula:

$$X_{ij}^{sim}(t_r+\Delta t) = X_{ij}^{\exp}(t_r-\Delta t) + 2\cdot\Delta t\cdot\sum_{k=1}^{n}(a_{ik}(t_r)\cdot X_{kj}^{\exp}(t_r)), \tag{3}$$

where *n* is the number of proteins at time point t_r, *m* is the number of samples and $a_{ik}(t_r)$ is the optimal solution of the optimization problem (6) in the main text, which denotes the interaction ability of the *k-th* protein to *i-th* protein at time point t_r. Δt stands for the time increment.

Moreover, the average values of AAEs and AREs were computed as follows. First, according to the definitions of the AAE and ARE, i.e. the equations (1) and (2), we calculated the AAE and ARE of the temporary network at each time point. Second, the AAEs and AREs were averaged across all the time points, which gave the errors for the constructed dynamic networks in the control condition and case condition, respectively.

2. Cross-validation

For each dataset, leaving one sample $S_i, i = 1, 2, \cdots, N$ out, we used the remaining $N-1$ samples for repeating the process of the construction of dynamic networks, where N represents the number of the subjects. Based on the reconstructed dynamic networks, we carried out the validation for the excluded sample S_i. Five measures were used to evaluate the results, including Sensitivity (SN), Specificity (SP), False positive rate (FPR), Accuracy (ACC) and Matthews coefficient constant (MCC). Mathematically, they are defined as follows[1,2]:

$$SN = TP / (TP + FN) \tag{4}$$

$$SP = TN / (TN + FP) \tag{5}$$

$$FPR = FP / (FP + TN) \tag{6}$$

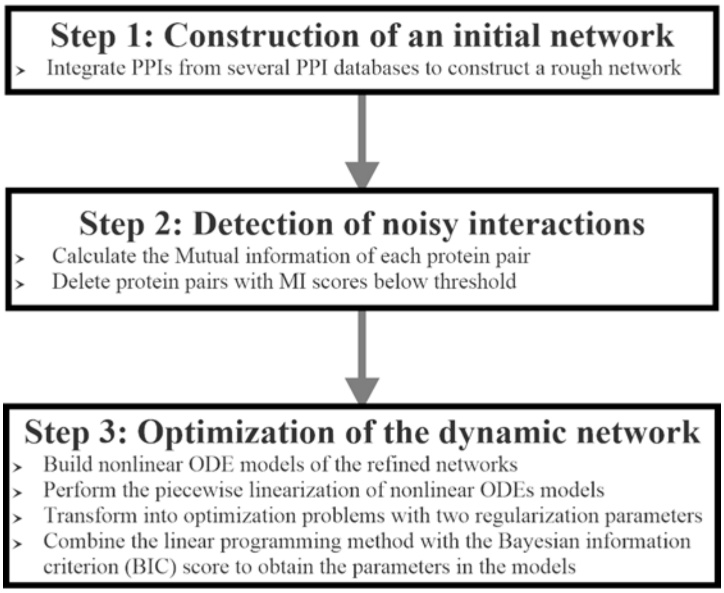
$$ACC = (TP + TN) / (TP + FP + TN + FN) \tag{7}$$

$$MCC = \frac{TP \cdot TN - FP \cdot FN}{\sqrt{(TP + FP)(TP + FN)(TN + FP)(TN + FN)}} \tag{8}$$

where TP (true positive) is the number of edges of the reconstructed dynamic network matched by the edges of the original dynamic network, FP (false positive) equals the total number of edges of the reconstructed dynamic network minus TP, TN (true negative) is the number of edges not in both the reconstructed dynamic network and the original dynamic network, and FN (false negative) is the number of edges of the original dynamic network that are not matched by the reconstructed dynamic network.

1. Fawcelt, T. An Introduction to ROC Analysis. *Pattern Recogn Lett* **27,** 861–874 (2006).
2. Zhang, X. *et al.* NARROMI: a noise and redundancy reduction technique improves accuracy of gene regulatory network inference. *Bioinformatics* **29**, 106-113 (2013).

Supplementary Figures:



Step 1: Construction of an initial network

- Integrate PPIs from several PPI databases to construct a rough network

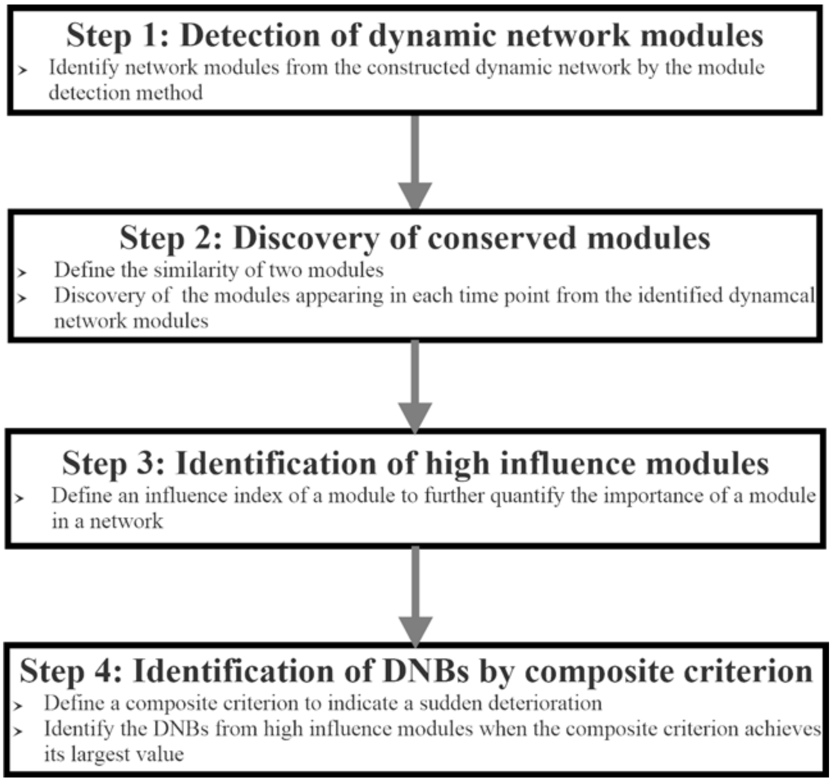
Step 2: Detection of noisy interactions

- Calculate the Mutual information of each protein pair
- Delete protein pairs with MI scores below threshold

Step 3: Optimization of the dynamic network

- Build nonlinear ODE models of the refined networks
- Perform the piecewise linearization of nonlinear ODEs models
- Transform into optimization problems with two regularization parameters
- Combine the linear programming method with the Bayesian information criterion (BIC) score to obtain the parameters in the models

Figure S1 | The framework of the network construction.



Step 1: Detection of dynamic network modules

- Identify network modules from the constructed dynamic network by the module detection method

Step 2: Discovery of conserved modules

- Define the similarity of two modules
- Discovery of the modules appearing in each time point from the identified dynamcal network modules

Step 3: Identification of high influence modules

- Define an influence index of a module to further quantify the importance of a module in a network

Step 4: Identification of DNBs by composite criterion

- Define a composite criterion to indicate a sudden deterioration
- Identify the DNBs from high influence modules when the composite criterion achieves its largest value

Figure S2 | The framework of dynamic network biomarker identification.

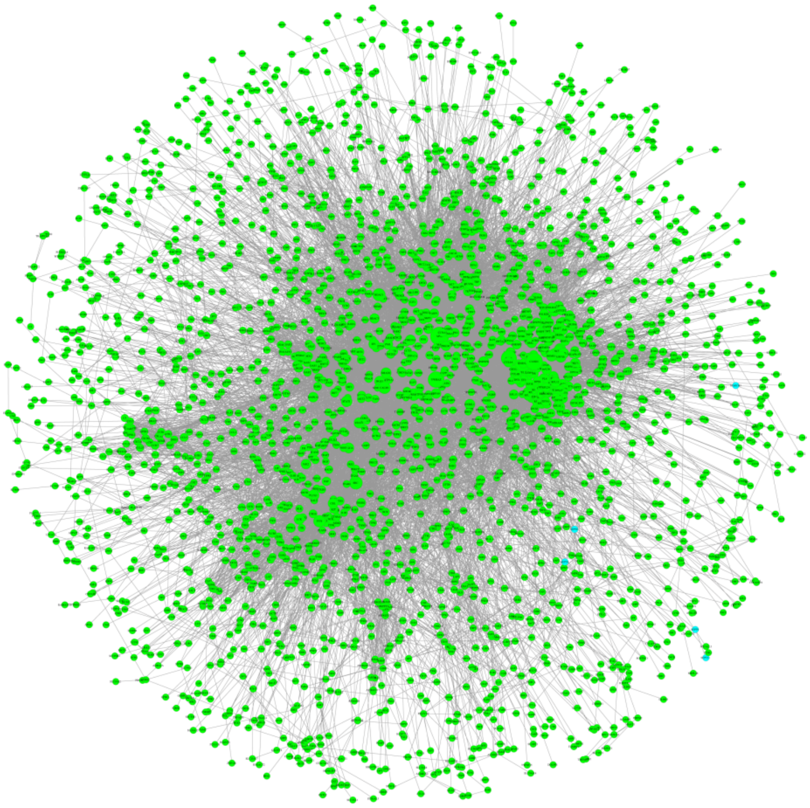


Figure S3 | An initial PPI network collected from three PPI databases (HPRD, BioGRID and STRING) for the datasets GSE30550 and GSE52428. We extracted high confidence (>0.7) interactions from the STRING database. In this network, there are 2400 nodes and 16498 edges. The node sizes are proportional to the degree of the nodes.

Figure S4 | An initial PPI network collected from three PPI databases (HPRD, BioGRID and STRING) for the dataset GSE2565. We extracted high confidence (>0.7) interactions from the STRING database. In this network, there are 770 nodes and 5890 edges. The node sizes are proportional to the degree of the nodes.

Figure S5 | An initial PPI network collected from three PPI databases (HPRD, BioGRID and STRING) for the dataset GSE13268. We extracted high confidence (>0.7) interactions from the STRING database. In this network, there are 755 nodes and 4054 edges. The node sizes are proportional to the degree of the nodes.

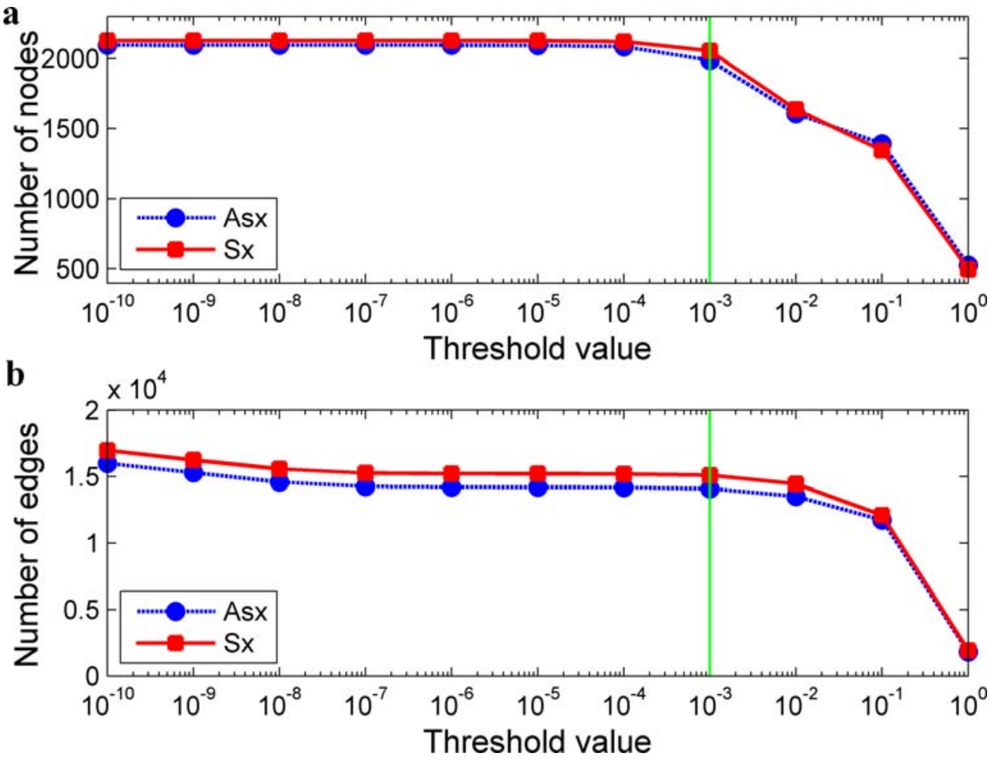


Figure S6 | The number of nodes and edges for various thresholds for the dataset GSE30550. Blue dashed line with circle markers and red solid line with square markers represent the number of nodes (a) and edges (b) in the asymptomatic (Asx) and symptomatic (Sx) networks, respectively. The green line indicates the threshold we chose in our study.

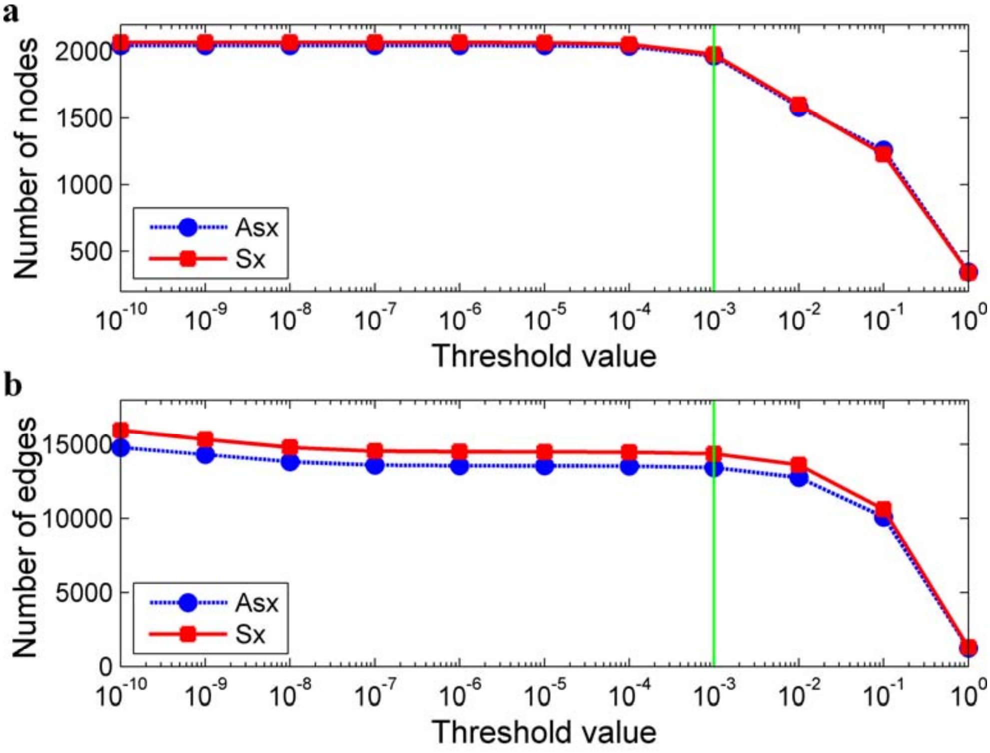


Figure S7 | The number of nodes and edges for various thresholds for the dataset GSE52428. Blue dashed line with circle markers and red solid line with square markers represent the number of nodes (a) and edges (b) in the asymptomatic (Asx) and symptomatic (Sx) networks, respectively. The green line indicates the threshold we chose in our study.

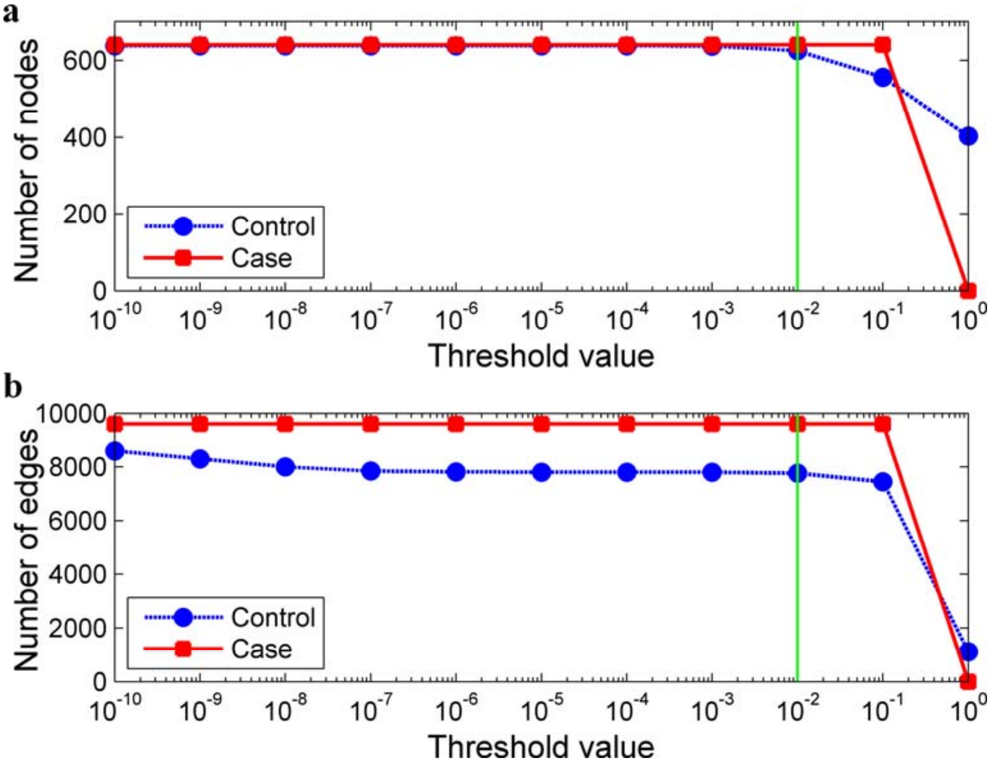


Figure S8 | The number of nodes and edges for various thresholds for the dataset GSE2565. Blue dashed line with circle markers and red solid line with square markers represent the number of nodes (a) and edges (b) in the control and case networks, respectively. The green line indicates the threshold we chose in our study.

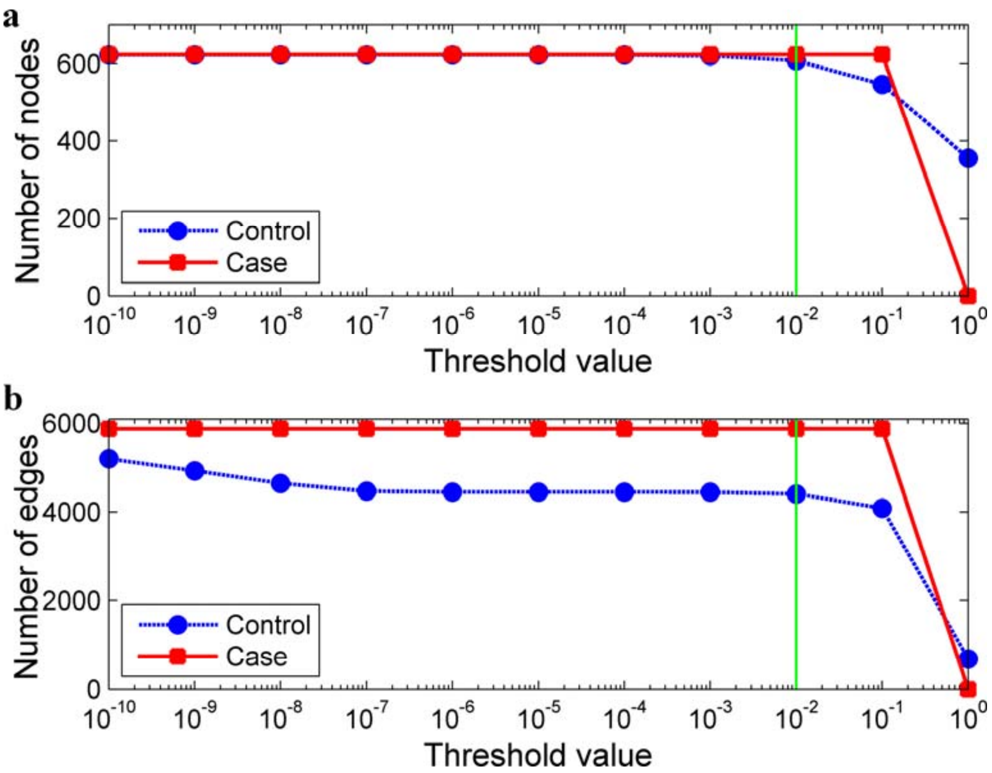


Figure S9 | The number of nodes and edges for various thresholds for the dataset GSE13268. Blue dashed line with circle markers and red solid line with square markers represent the number of nodes (a) and edges (b) in the control and case networks, respectively. The green line indicates the threshold we chose in our study.

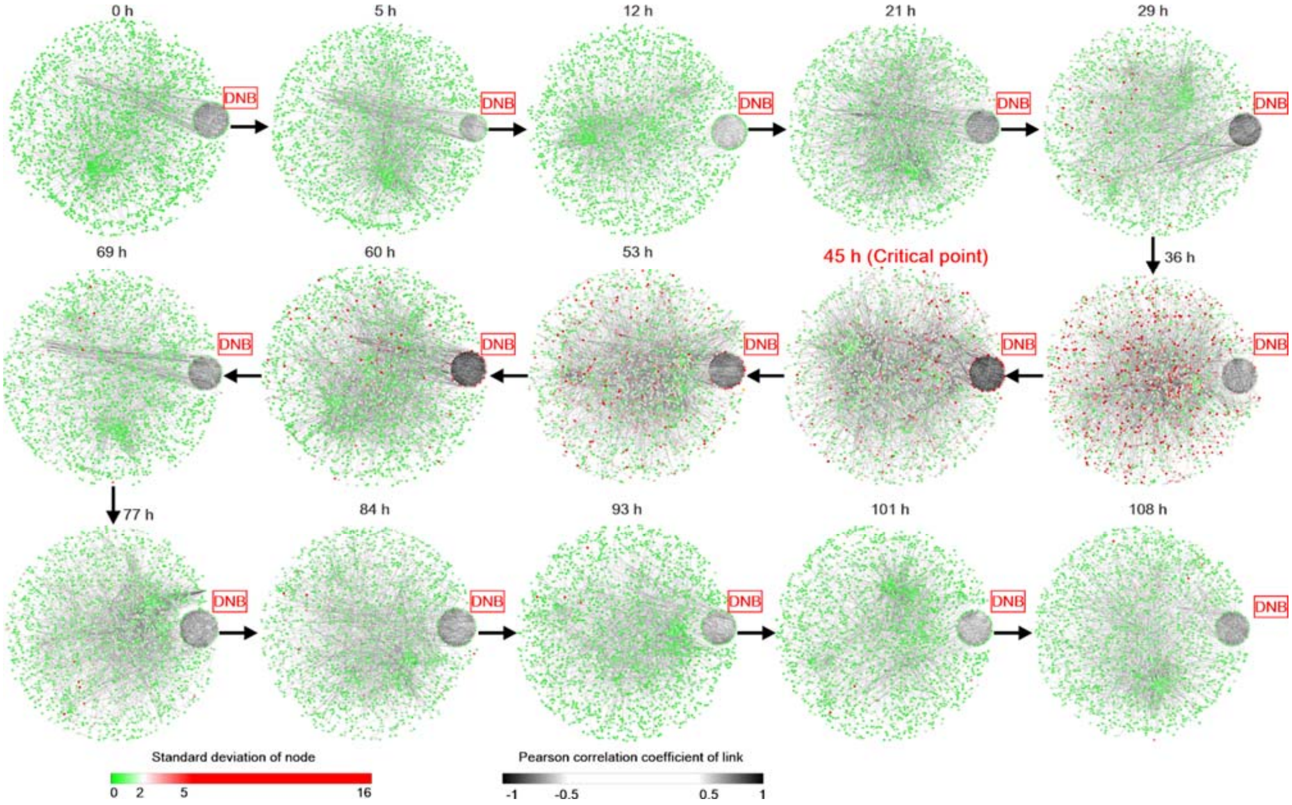


Figure S10 | Dynamical changes in the constructed symptomatic network for the dataset GSE30550, including the detected DNB during the disease progression for the live H3N2 influenza infection. The DNBs are highlighted in the small circle. We show the dynamical evolution of the network structure for the constructed molecular interaction network at 16 time points, i.e. 0h, 5h, 12h, 21h, 29h, 36h, 45h, 53h, 60h, 69h, 77h, 84h, 93h, 101h, and 108h. The color of the nodes represents the fluctuation strength of molecular expressions, and each edge represents the correlation between two nodes. It can be seen that at 45 hour, there is a strong signal to indicate the pre-disease state or pre-symptom. From these figures showing the dynamic evolution, it is obvious that the group of DNB not only provides significant signals as the system approaches the critical point, but also forms a strongly correlated observable subnetwork in terms of expression variations and network connections.

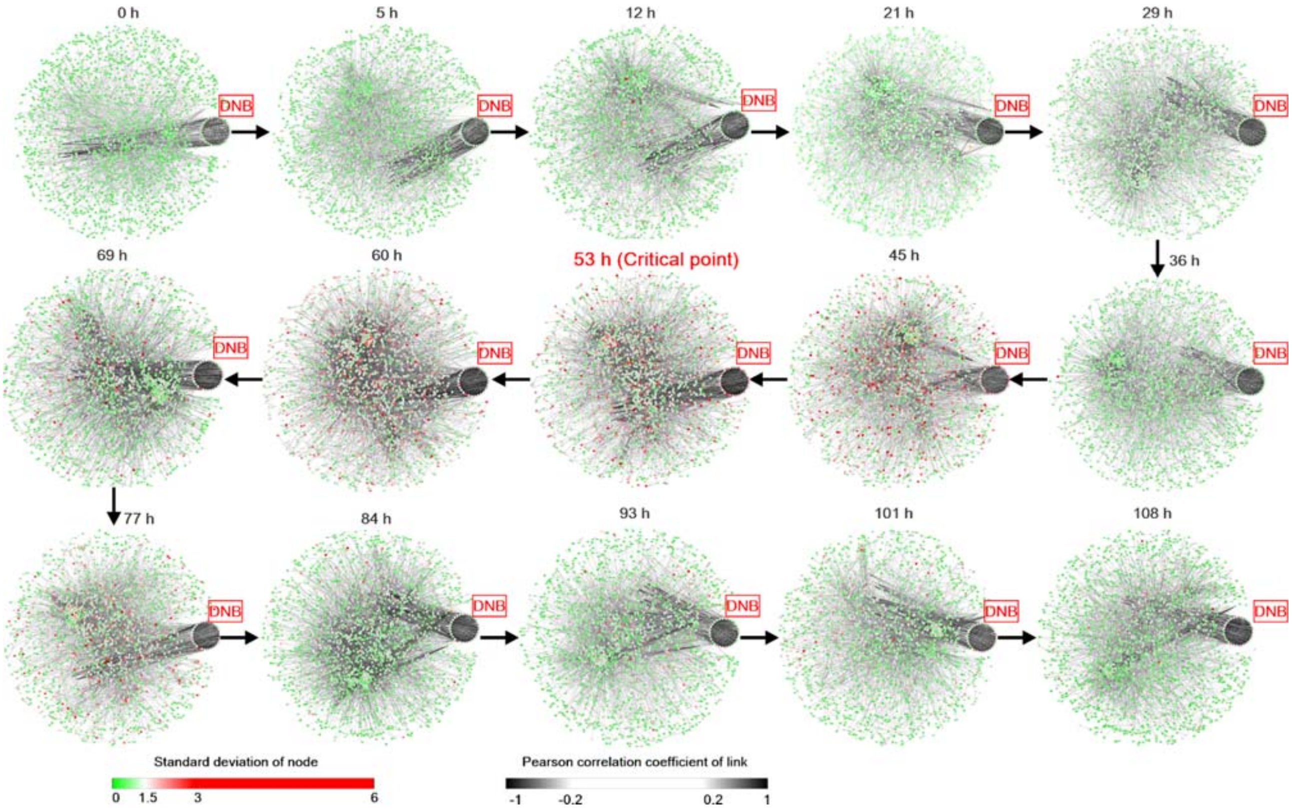


Figure S11 | Dynamical changes in the constructed symptomatic network for the dataset GSE52428, including the detected DNB during the disease progression for the live H1N1 influenza infection. The DNBs are highlighted in the small circle. We show the dynamical evolution of the network structure for the constructed molecular interaction network at 16 time points, i.e. 0h, 5h, 12h, 21h, 29h, 36h, 45h, 53h, 60h, 69h, 77h, 84h, 93h, 101h, and 108h. The color of the nodes represents the fluctuation strength of molecular expressions, and each edge represents the correlation between two nodes. It can be seen that at 53 hour, there is a strong signal to indicate the pre-disease state or pre-symptom.

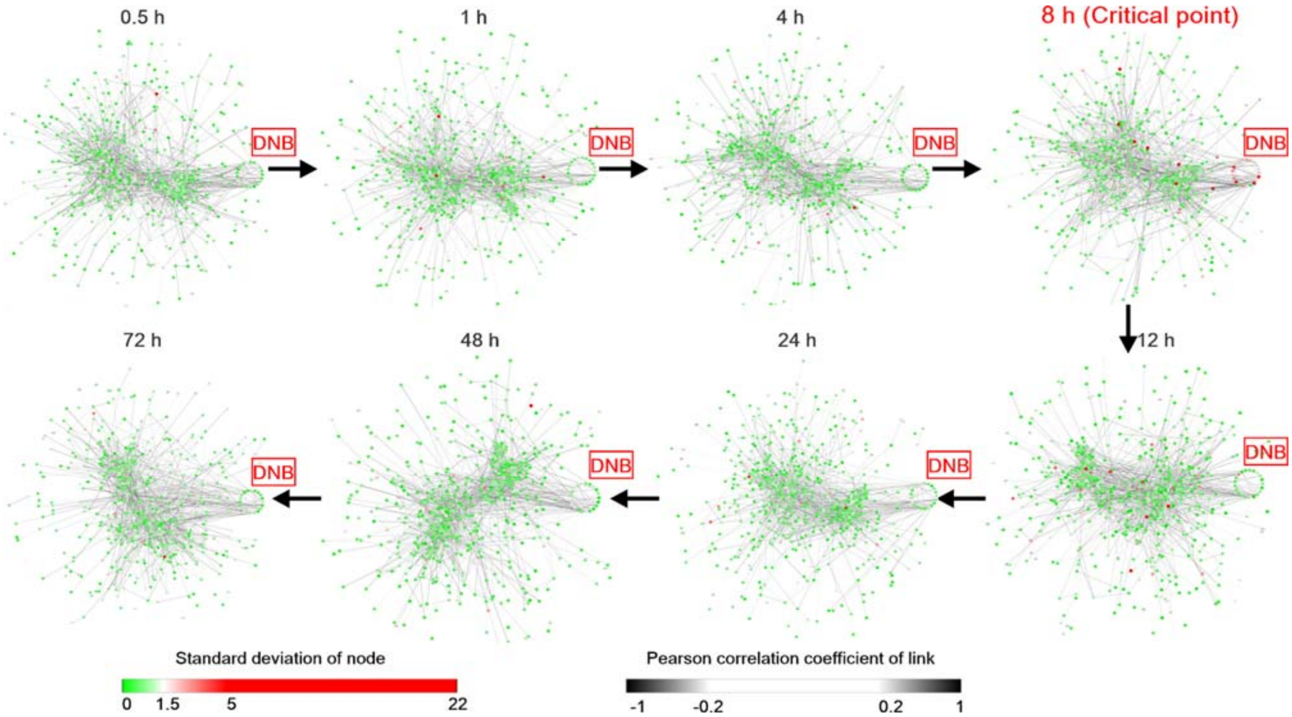


Figure S12 | Dynamical changes in the constructed case network for the dataset GSE2565, including the detected DNB during the disease progression for the acute lung injury. The DNBs are highlighted in the small circle. We show the dynamical evolution of the network structure for the constructed molecular interaction network at 8 time points, i.e. 0.5h, 1h, 4h, 8h, 12h, 24h, 48h, and 72h. The color of the nodes represents the fluctuation strength of molecular expressions, and each edge represents the correlation between two nodes. It can be seen that at 8 hour, there is a strong signal to indicate the pre-disease state.

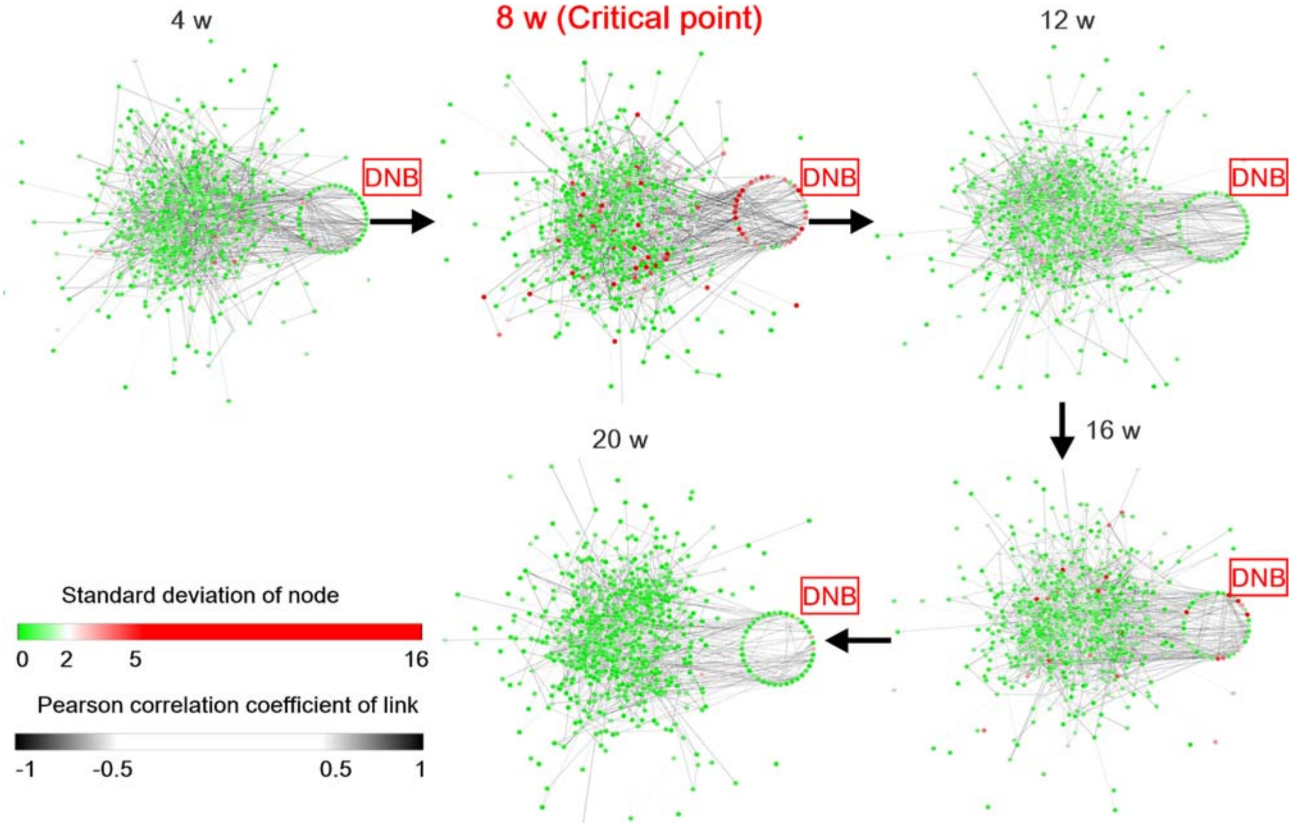


Figure S13 | Dynamical changes in the constructed case network for the dataset GSE13268, including the detected DNB during the disease progression for the type 2 diabetes mellitus. The DNBs are highlighted in the small circle. We show the dynamical evolution of the network structure for the constructed molecular interaction network at 5 time period, i.e. 4 week, 8 week, 12 week, 16 week, and 20 week. The color of the nodes represents the fluctuation strength of molecular expressions, and each edge represents the correlation between two nodes. It can be seen that at the 8 week, there is a strong signal to indicate the pre-disease state.

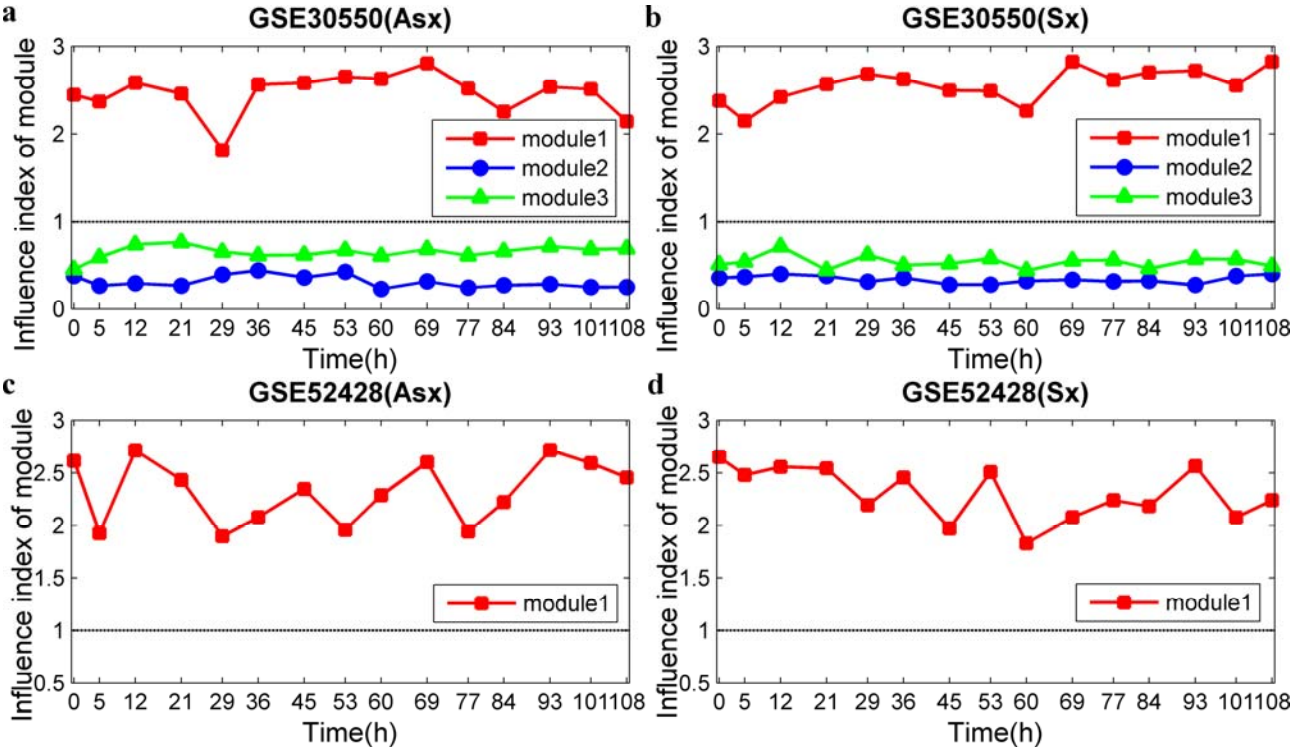


Figure S14 | Influence index of a module (IIM) of common modules respectively for dataset GSE30550 and GSE52428. (a) Three modules in the asymptomatic network (Asx) for GSE30550 dataset. (b) Three modules in the symptomatic network (Sx) for GSE30550 dataset. (c) One module in the asymptomatic network (Asx) for GSE52428 dataset. (d) One module in the symptomatic network (Sx) for GSE52428 dataset.

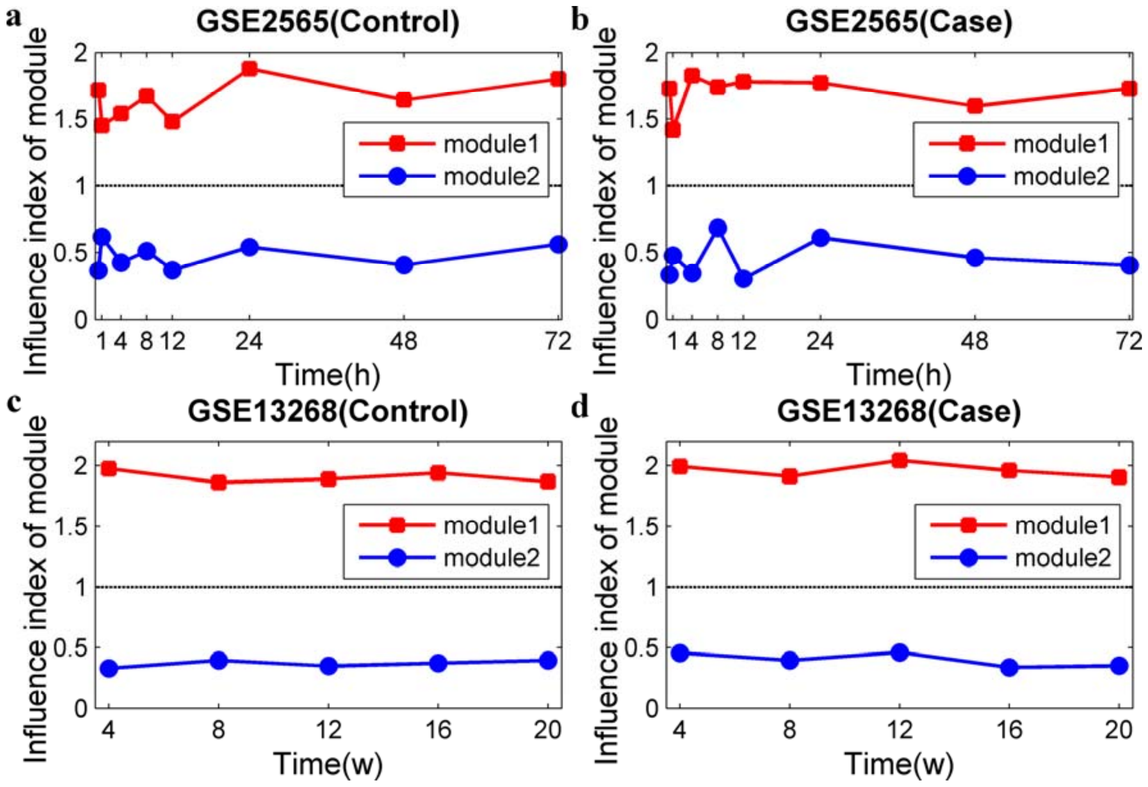


Figure S15 | Influence index of a module (IIM) of common modules respectively for the datasets GSE2565 and GSE13268. (a) Two modules in the control network for the GSE2565 dataset. (b) Two modules in the case network for the GSE2565 dataset. (c) Two modules in the control network for the GSE13268 dataset. (d) Two modules in the case network for the GSE13268 dataset.

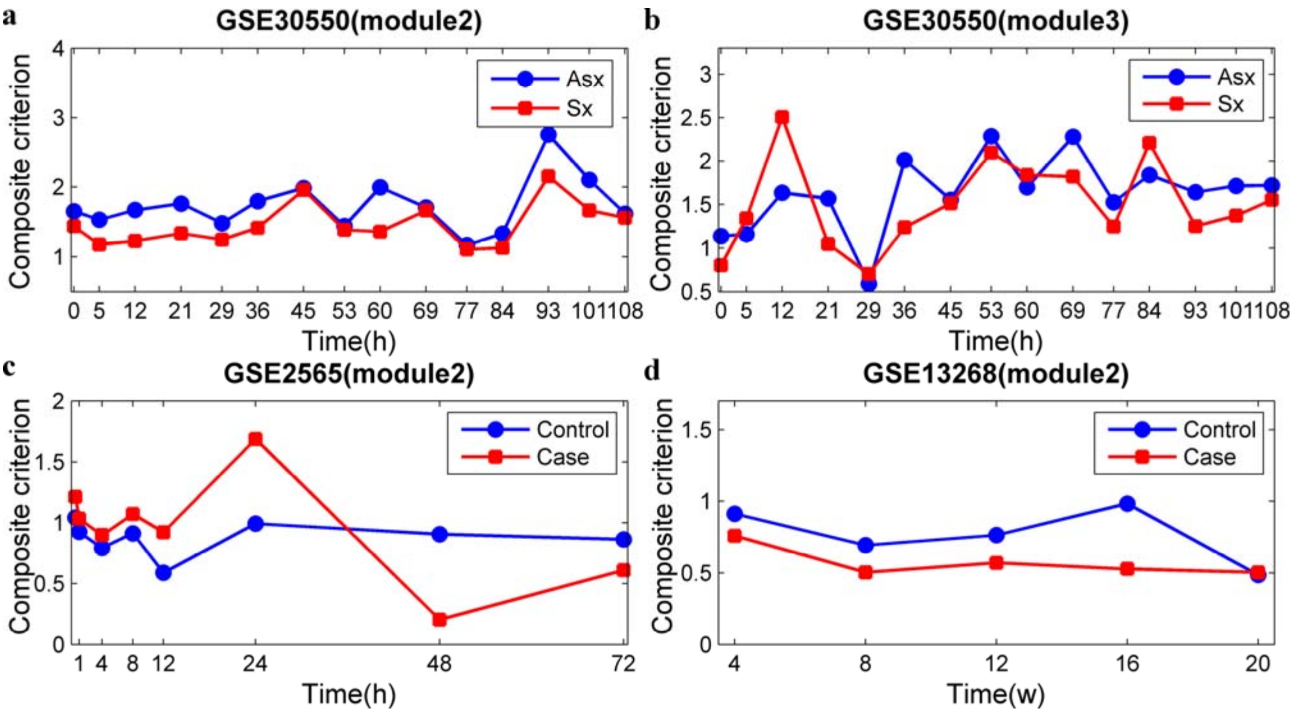


Figure S16 | Comparisons of composite criterions (CCs) of other common modules between the control (Asx) and case (Sx) networks for the four sets of high-throughput experimental data. (a) Module 2 in the GSE30550 dataset; (b) Module 3 in the GSE30550 dataset; (c) Module 2 in the GSE2565 dataset; (d) Module 2 in the GSE13268 dataset. Blue line with circle markers and red line with square markers represent composite criterion of the control (asymptomatic (Asx)) and case (symptomatic (Sx)) networks, respectively. There are no strong and significant early-warning signals of these modules before the diseases are eventually deteriorated.

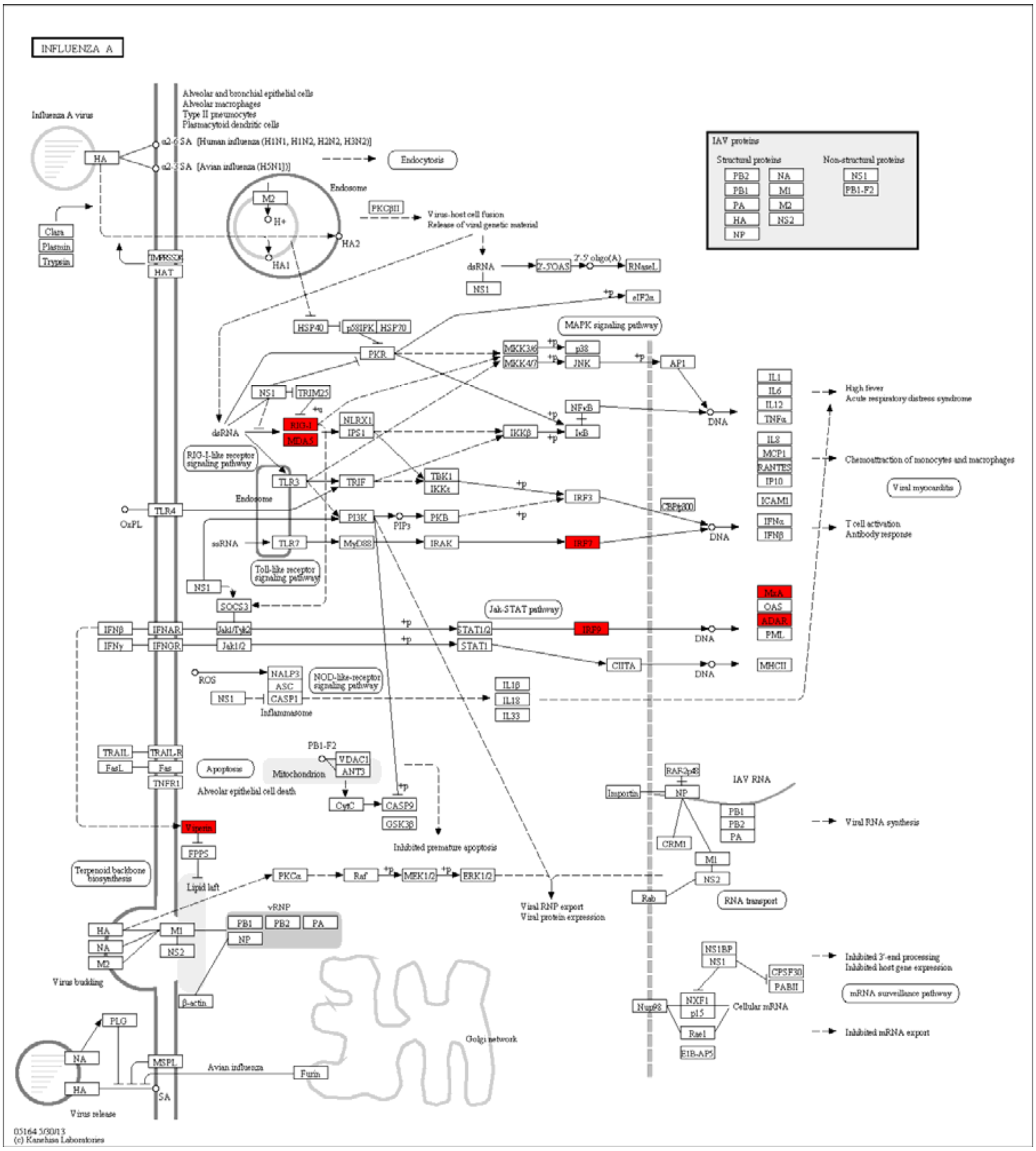


Figure S17 | Influenza A pathway enriched by DNB genes in red color. The red marked genes are DDX58 (RIG-I), MX1, OAS1, OAS2, OAS3, IFIH1 (MDA5) and RASD2 (Viperin).

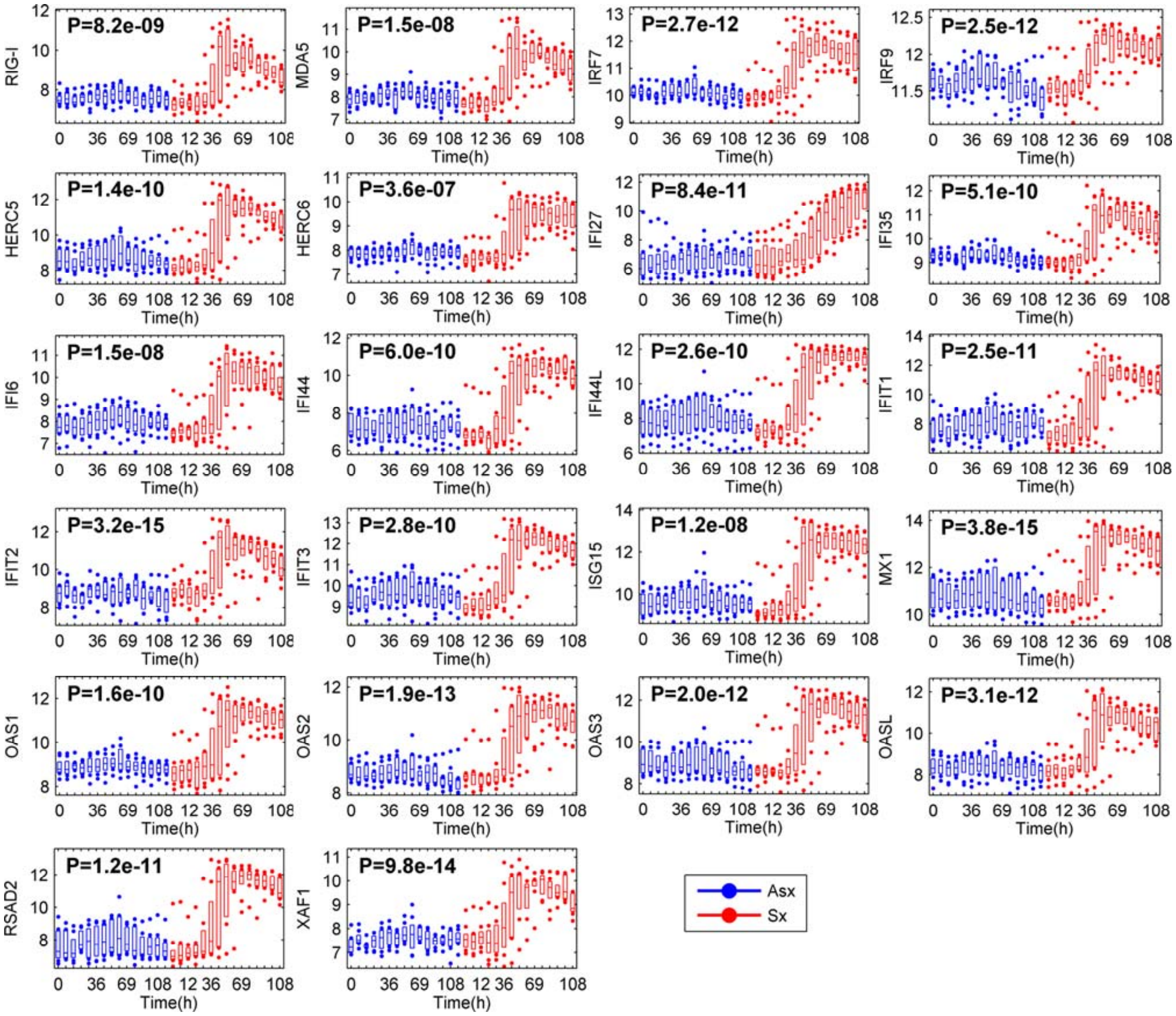


Figure S18 | Comparison of expression values of the identified DNBs in the symptomatic infection (Sx) with those in the asymptomatic infection (Asx) for the H3N2 strain. Blue and red lines indicate Asx and Sx, respectively. P-values are from a two-tailed Wilcoxon rank sum test. The results reveal that DNBs exhibit significant higher levels in the symptomatic infections than those in the asymptomatic infections (P-values < 0.0001).

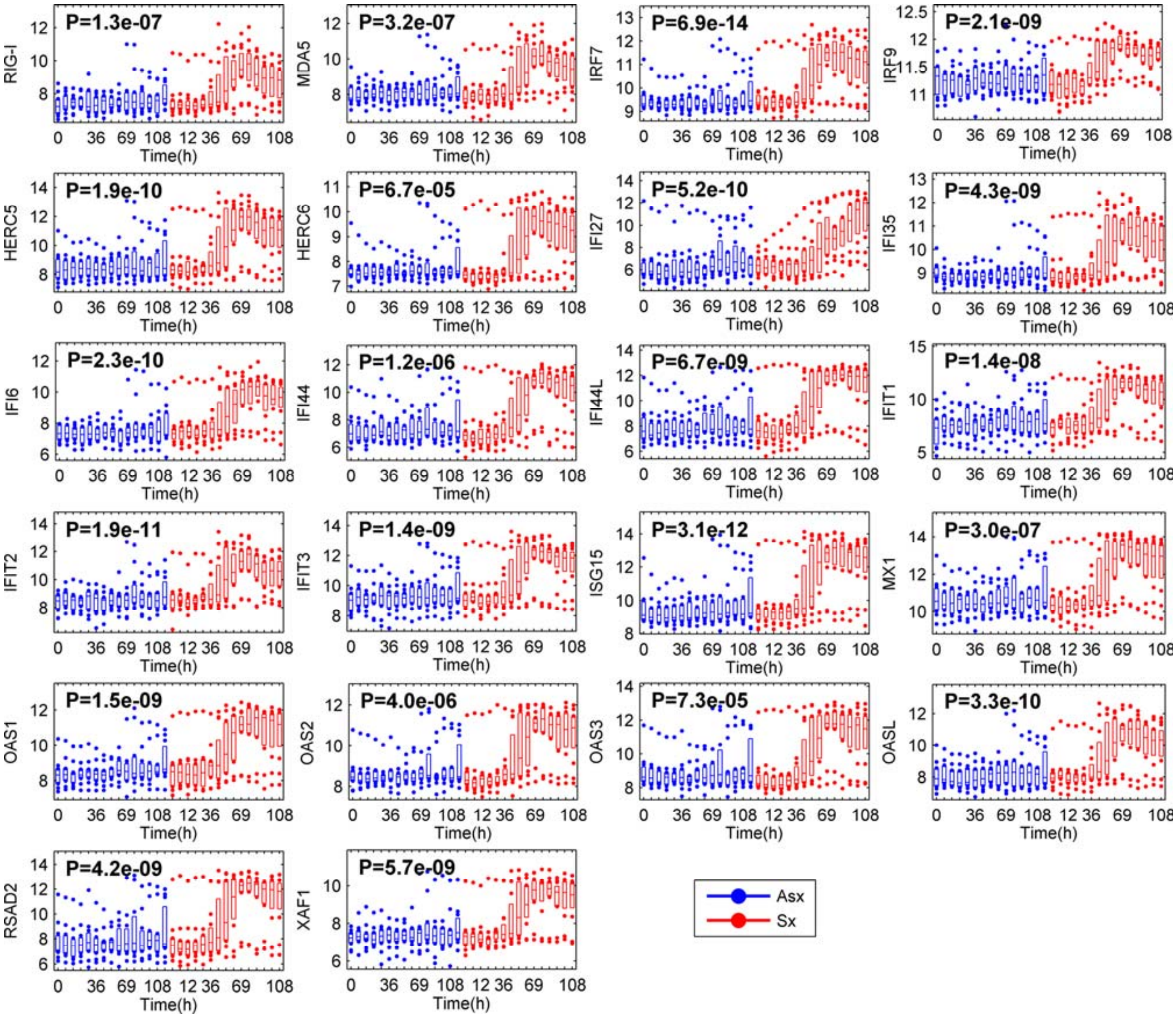


Figure S19 | Comparison of expression values of the identified DNBs in the symptomatic infection (Sx) with those in the asymptomatic infection (Asx) for the H1N1 strain. Blue and red lines indicate Asx and Sx, respectively. P-values are from a two-tailed Wilcoxon rank sum test. The results reveal that DNBs exhibit significant higher levels in the symptomatic infections than those in the asymptomatic infections (P-values < 0.0001).

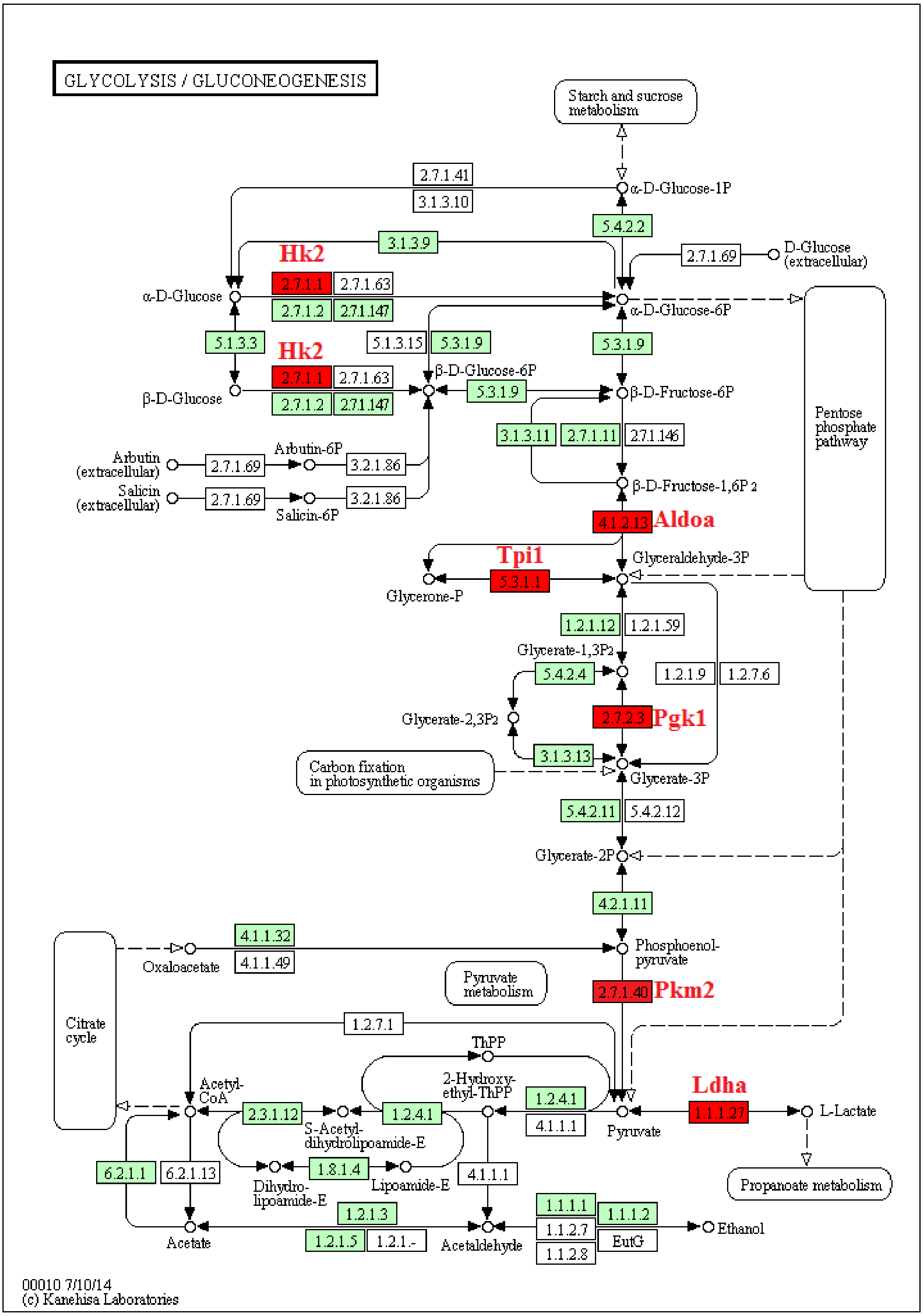


Figure S20 | Glycolysis / Gluconeogenesis pathway enriched by DNB genes in red color. The red marked genes in the figure are Hk2, Aldoa, Ldha, Pgk1, Pkm2 and Tpi1.

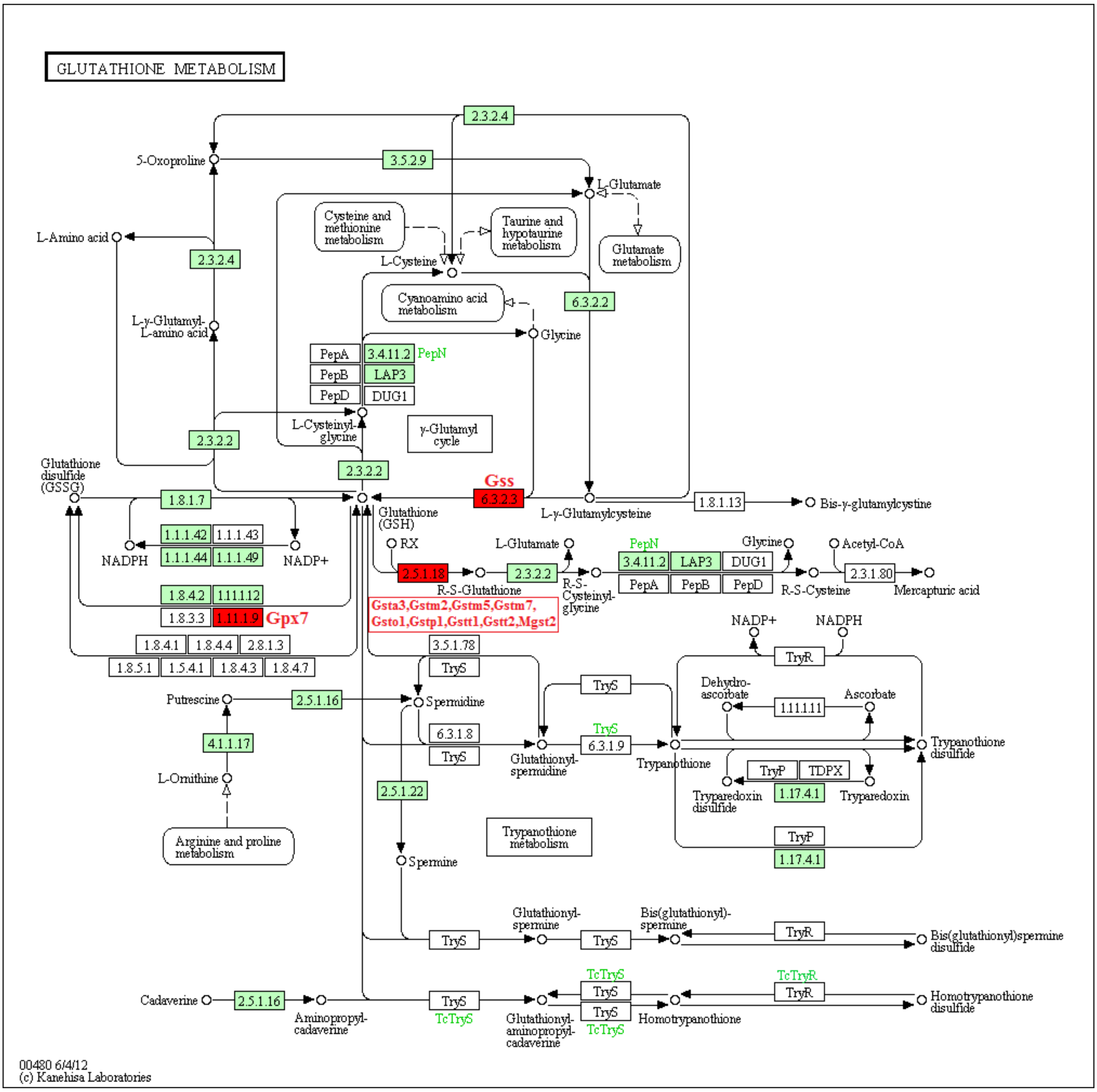


Figure S21 | Glutathione metabolism pathway enriched by DNB genes in red color. The red marked genes in the figure are Gpx7, Gss, Gsta3, Gstm2, Gstm5, Gstm7, Gsto1, Gstp1, Gstt1, Gstt2 and Mgst2.

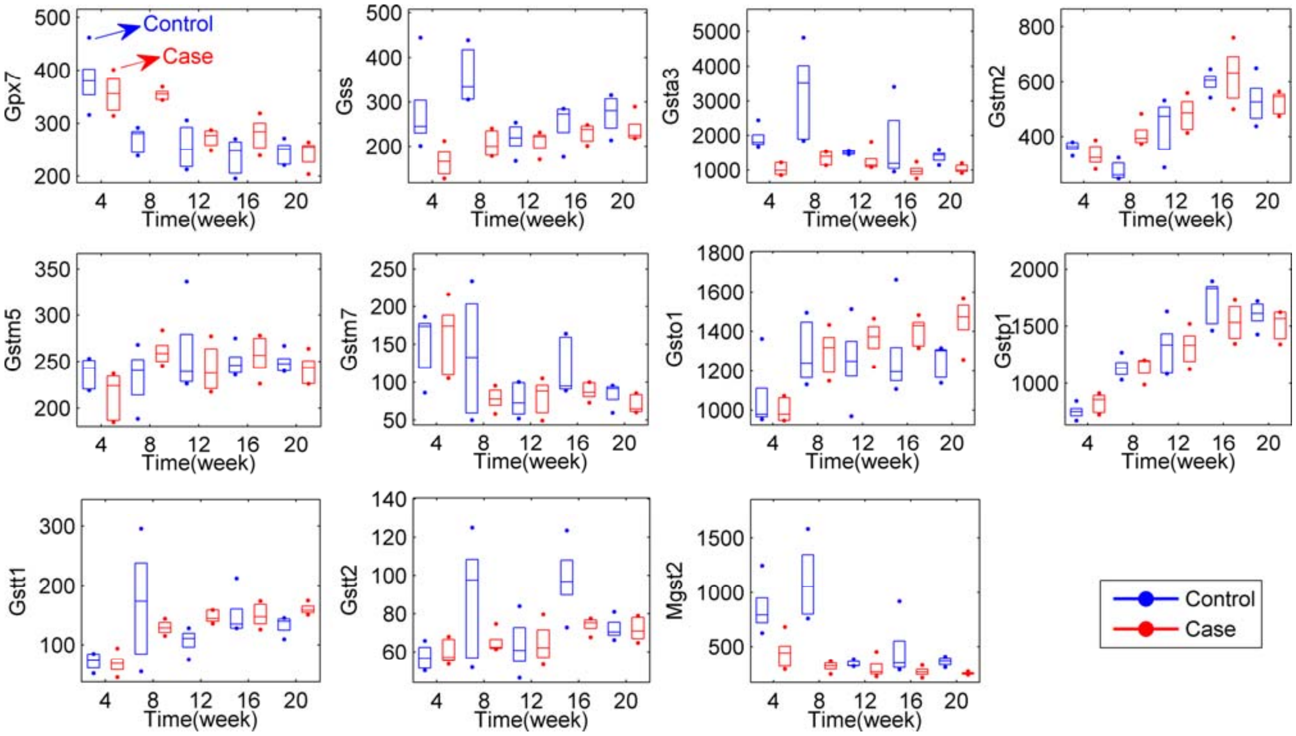


Figure S22 | Comparison of expression values of the DNB genes (enriched in the Glutathione metabolism pathway) in the control with those in the case for the type 2 diabetes mellitus. Blue and red lines indicate control and case, respectively. The results reveal that most of these genes exhibit lower concentrations at almost each period in the diabetic subjects than those in the control subjects, except for Gpx7, Gstm2, Gsto1 and Gstt1.

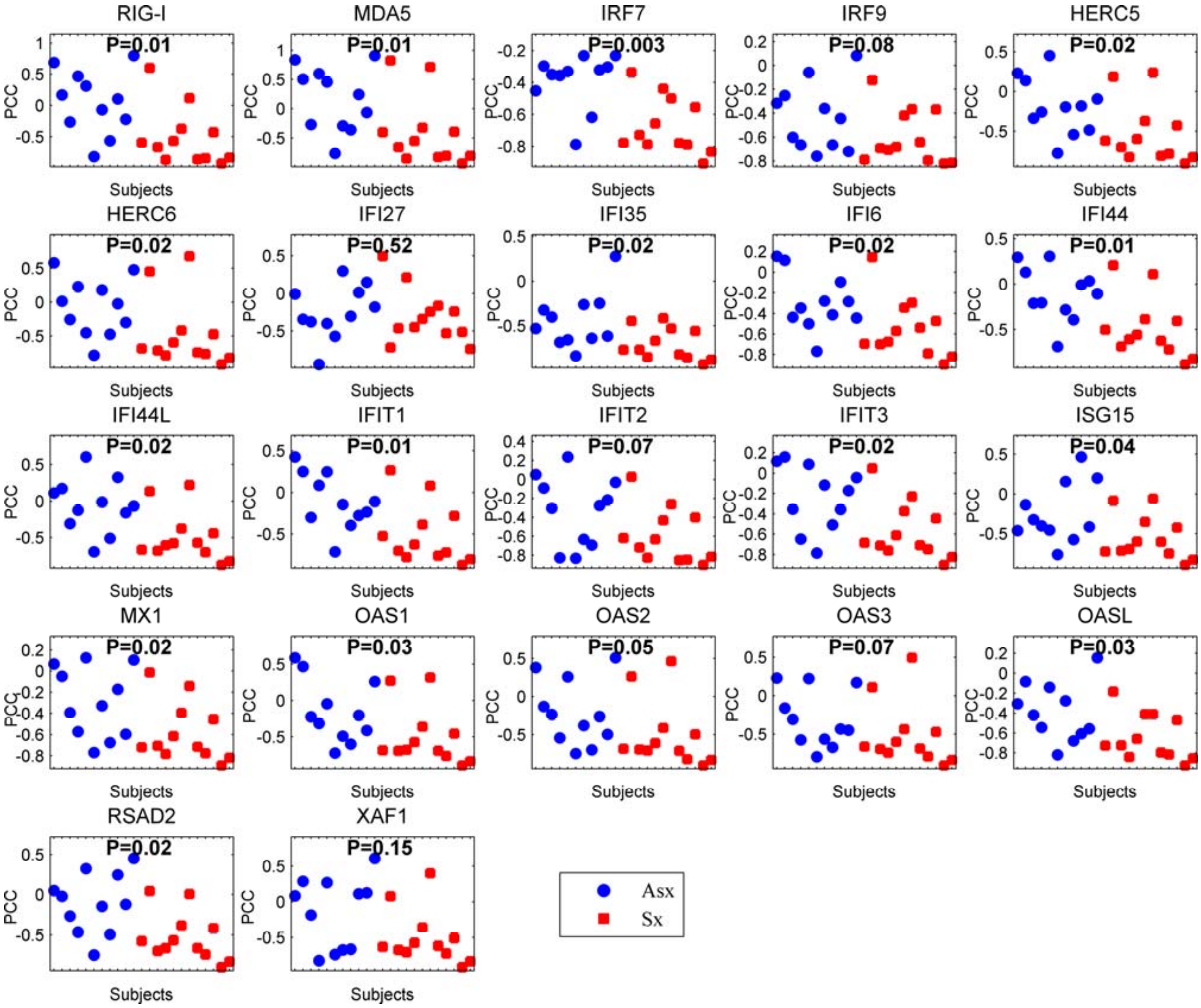


Figure S23 | Comparison of the distributions of correlations between the expression values of S1PR1 and those of DNBs for the H1N1 strain. Blue circles and red squares indicate Pearson correlation coefficient (PCC) between the expression values of S1PR1 and those of DNBs in the asymptomatic infection (Asx) with those in the symptomatic infection (Sx), respectively. X-axis represents the Asx or Sx subjects, namely control or case groups. Each data point corresponds to a correlation in one subject. P-values are from a two-tailed Wilcoxon rank sum test.

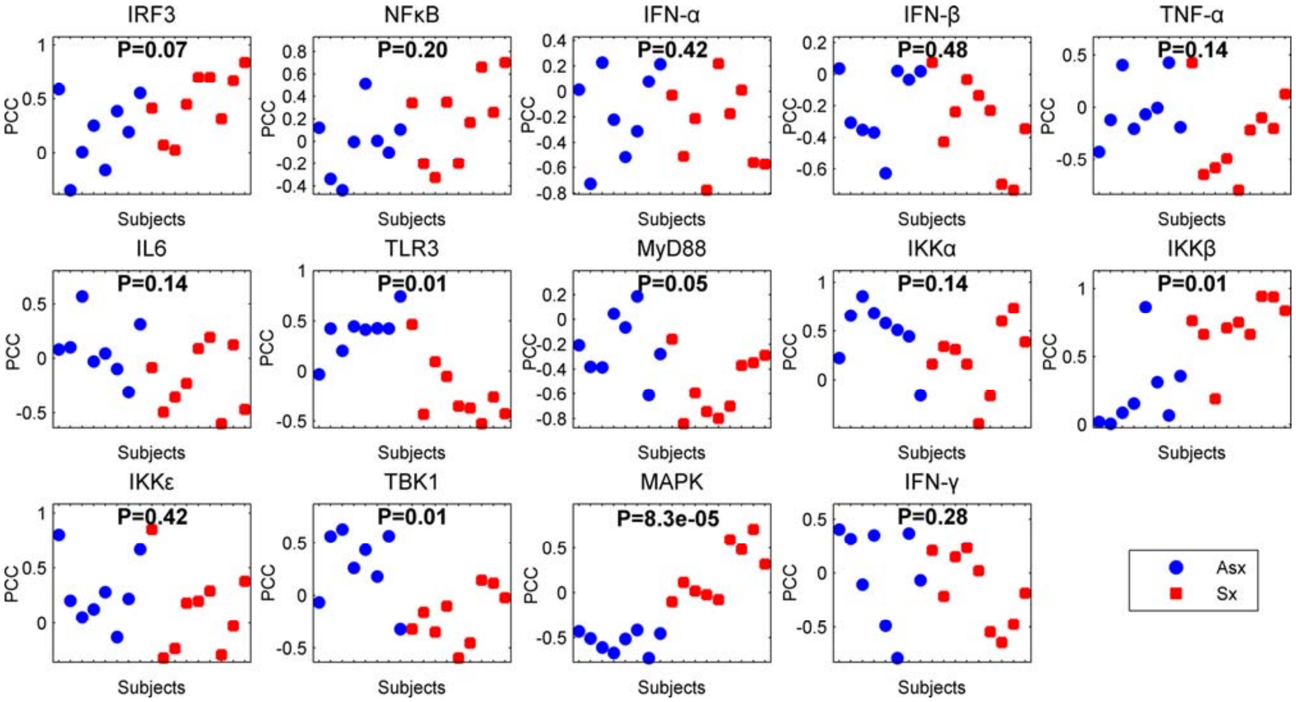


Figure S24 | Comparison of the distributions of correlations between the expression values of S1PR1 and those of other 14 critical proteins for the H3N2 strain. Blue circles and red squares indicate Pearson correlation coefficient (PCC) between the expression values of S1PR1 and those of other 14 critical proteins of innate immunity response in the asymptomatic infection (Asx) with those in the symptomatic infection (Sx), respectively. P-values are from a two-tailed Wilcoxon rank sum test. The difference between the distributions of correlations of the two clinical outcomes was not significant for the H3N2 strain (most of the P-values are larger than 0.05).

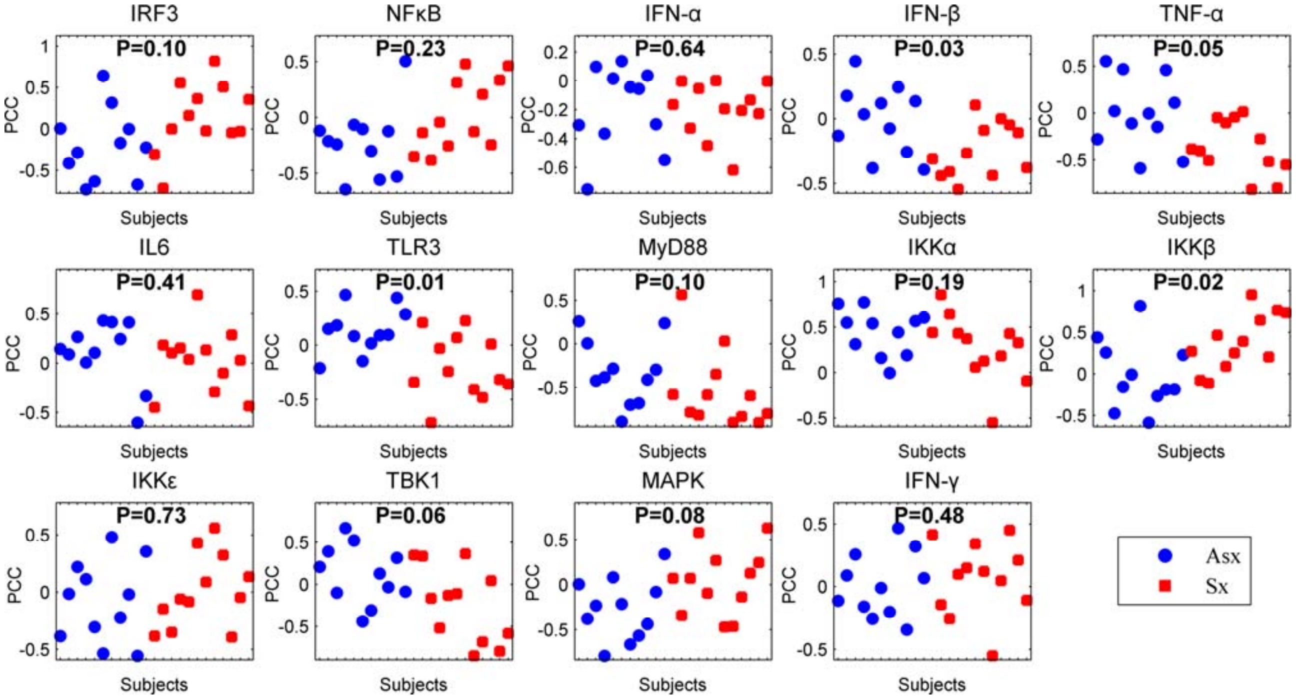


Figure S25 | Comparison of the distributions of correlations between the expression values of S1PR1 and those of other 14 critical proteins for the H1N1 strain. Blue circles and red squares indicate Pearson correlation coefficient (PCC) between the expression values of S1PR1 and those of other 14 critical proteins of innate immunity response in the asymptomatic infection (Asx) with those in the symptomatic infection (Sx), respectively. P-values are from a two-tailed Wilcoxon rank sum test. The difference between the distributions of correlations of the two clinical outcomes was not significant for the H1N1 strain (most of the P-values are larger than 0.05).

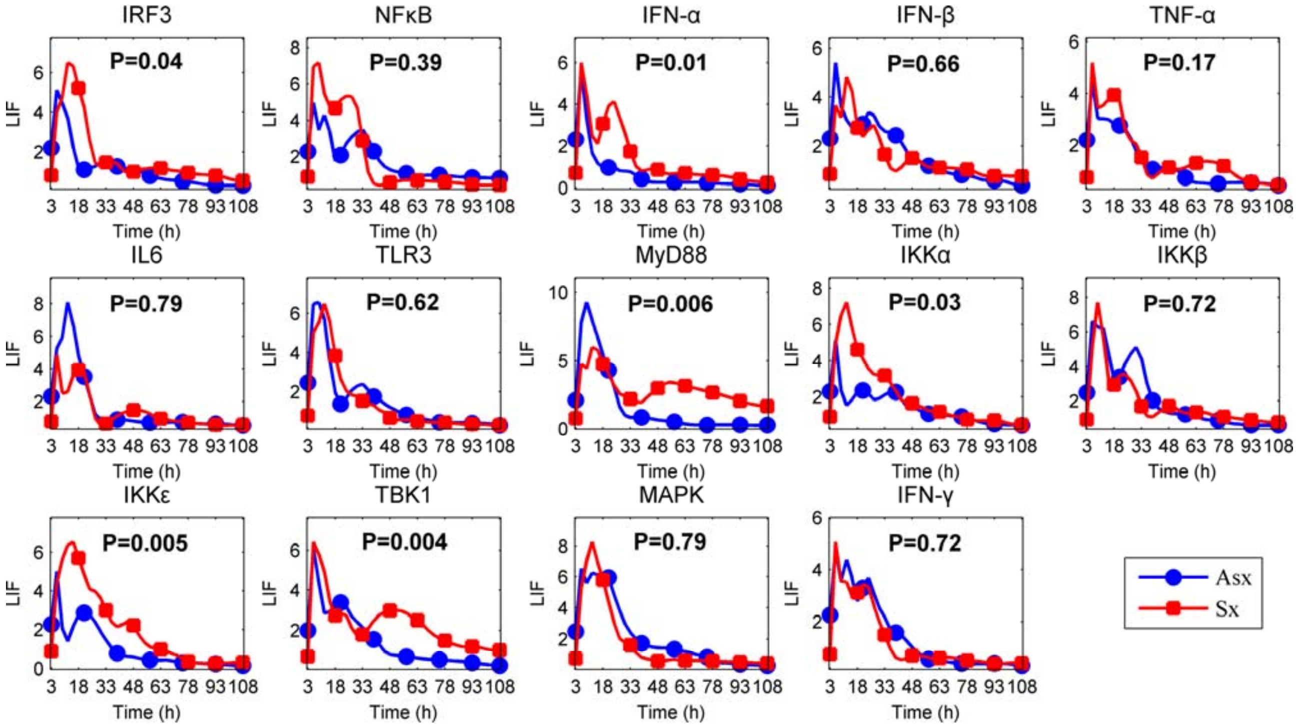


Figure S26 | Comparison of the local information flows (LIF) transmission from virus to other 14 key proteins of innate immunity response in the symptomatic subjects (Sx) and the asymptomatic subjects (Asx) infected by the H3N2 influenza strain. The blue and red lines denote the local information flows in Asx and Sx, respectively. Through performing a two-sample t-test, we showed that the local information flows exhibited no significantly differences between Asx and Sx, except for MyD88, IKKε and TBK1.

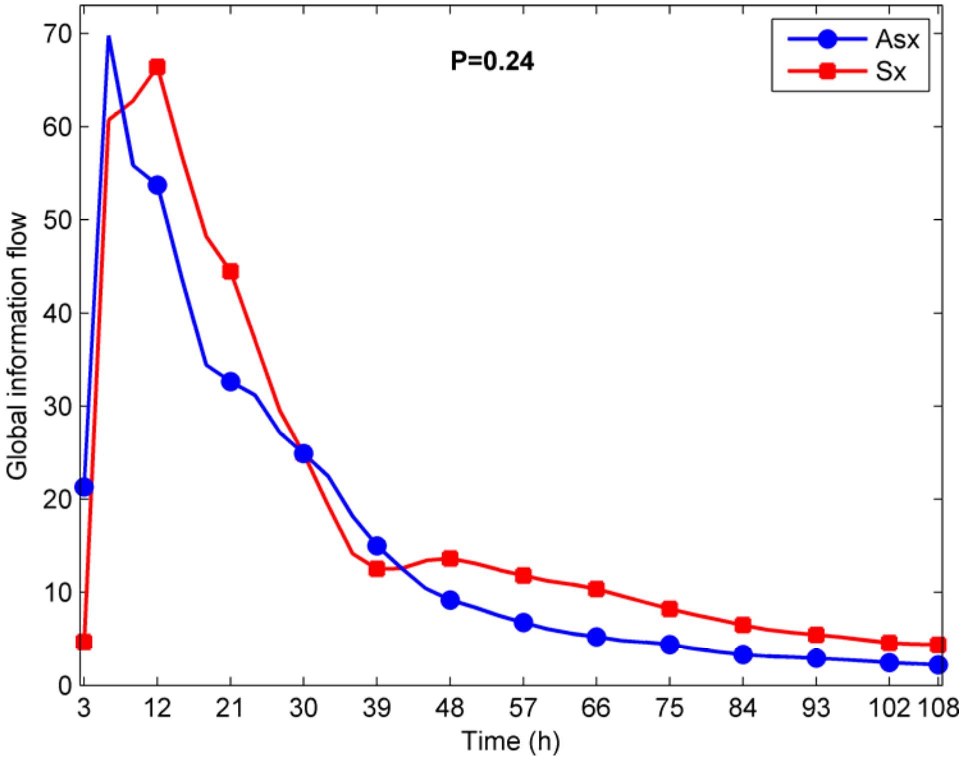


Figure S27 | Comparison of the global information flows transmission from virus to other 14 key proteins of innate immunity response in the symptomatic subjects (Sx) and the asymptomatic subjects (Asx) infected by the H3N2 influenza strain. P-value is from a two-sample t-test. The blue and red lines denote the global information flows in Asx and Sx, respectively. The result showed that there are not significant differences in the global information flows between Asx and Sx (P-value = 0.24).

Supplementary Tables:

Table S1 The 2400 proteins selected in the datasets GSE30550 and GSE52428

Symbol	Symbol	Symbol	Symbol	Symbol	Symbol	Symbol	Symbol
ABCA5	CCBL1	ECHS1	HIST1H4L	MICB	PEX3	RPL8	TCEA2
ABCB1	CCBL2	ECI2	HIST3H3	MICU1	PEX5	RPLP1	TCEAL1
ABCB11	CCDC130	ECM1	HIVEP3	MIF	PFAS	RPLP2	TCEAL4
ABCB4	CCDC33	EDC4	HK3	MIIP	PFKFB3	RPP14	TCERG1
ABCB7	CCDC9	EDEM1	HLA-A	MINA	PFKM	RPS11	TCF20
ABCB8	CCL11	EDEM2	HLTF	MIOS	PFN1	RPS13	TCF25
ABCC1	CCL13	EDF1	HMG20A	MIPEP	PFN2	RPS14	TCF7
ABCC3	CCL2	EDNRA	HMGN1	MIS12	PGAP3	RPS16	TCF7L2
ABCC5	CCL22	EDNRB	HMGN3	MKKS	PGM5	RPS19	TCL1A
ABCD1	CCL25	EED	HMHA1	MKL2	PHACTR2	RPS2	TCN2
ABCD2	CCL5	EEF1D	HMOX1	MKLN1	PHB2	RPS20	TCP1
ABCD4	CCL7	EEF2	HMOX2	MKNK2	PHF10	RPS21	TCP11
ABCE1	CCL8	EFHC1	HN1L	MKRN2	PHF11	RPS23	TDP1
ABHD10	CCNA1	EFHC2	HNF1A	MLH1	PHF15	RPS24	TDRD3
ABLIM1	CCNC	EFNB1	HNRNPA0	MLLT11	PHF16	RPS3	TDRD7
ABLIM3	CCND2	EGF	HNRNPA1	MLLT3	PHF21A	RPS4X	TENC1
ABT1	CCNG1	EGFL7	HNRNPC	MLXIP	PHLDA2	RPS5	TERF1
ABTB2	CCNG2	EGLN2	HNRNPD	MMS19	PHLPP2	RPS6	TESPA1
ACAA2	CCNL2	EGR1	HNRNPDL	MOAP1	PI4KA	RPS6KA2	TEX10
ACACA	CCR1	EGR3	HNRNPK	MOCS2	PIAS2	RPS6KA3	TFAP2B
ACAD8	CCR10	EGR4	HNRNPR	MORC4	PIBF1	RPS6KA5	TFB2M
ACADS	CCR6	EHBP1	HNRNPUL1	MORF4L1	PIK3C2B	RPS9	TFEC
ACAP1	CCR7	EHD4	HOMER1	MPDU1	PIK3R1	RRAS	TGDS
ACAT2	CCSER2	EI24	HOXA3	MPHOSPH10	PIK3R4	RRAS2	TGFB1I1
ACKR2	CCT3	EIF1AX	HOXB2	MPI	PIKFYVE	RRBP1	TGIF1
ACKR3	CCT4	EIF2AK2	HOXC6	MPP5	PILRA	RREB1	TGM4
ACO1	CCT7	EIF2AK3	HPGD	MPRIP	PILRB	RRM1	THADA
ACP2	CD101	EIF2B3	HPSE	MRFAP1L1	PIN1	RRP15	THAP11
ACP6	CD14	EIF2D	HPSE2	MRPL20	PIP4K2C	RRP1B	THBS1
ACTG1	CD163	EIF3A	HR	MRPL24	PJA1	RRS1	THEMIS2
ACTL6A	CD19	EIF3D	HS2ST1	MRPL3	PKIA	RSAD1	THY1
ACTL6B	CD2	EIF3E	HSD11B1	MRPL48	PKMYT1	RSAD2	TICAM1
ACTR1B	CD209	EIF3G	HSD17B12	MRPL9	PKP4	RSBN1	TIMM10
ACTR2	CD22	EIF3H	HSD17B4	MRPS15	PLA2G15	RSL1D1	TIMM22
ACTR3B	CD226	EIF3J	HSD17B8	MRPS2	PLAC8	RSRC1	TIMM9
ACTR5	CD244	EIF3K	HSF2	MRPS27	PLAG1	RTCB	TIMP2
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HERPUD1
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MGAT1
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TARDBP
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TBKBP1
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Table S2 The 770 proteins selected in the dataset GSE2565

Symbol	Symbol	Symbol	Symbol	Symbol	Symbol	Symbol	Symbol
Aars	Cd3g	Eg383901	Hipk2	Loc672215	Osmr	Rfpl4	Tek
Abcc1	Cd4	Eg545124	Hk2	Loc677317	Ottmusg00000014672	Rgs11	Tex10
Abcd3	Cd48	Eg627245	Hmga1	Loc677319	Ottmusg00000015538	Rhoj	Tfpi2
Abhd14a	Cd68	Eg665937	Hmgcs1	Lox	Papolg	Rhou	Tgds
Ablim1	Cd79a	Eg666031	Hmgxb3	Lpl	Pard6b	Rin1	Tgfb1i1
Acadl	Cd9	Eg667723	Hmox1	Lrg1	Pcf11	Ripk4	Tgif1
Acadvl	Cdc45l	Egr1	Hnrnpul2	Lrp2	Pcx	Rnasek	Tgm2
Acot10	Cdca5	Egr2	Homer2	Lrrc41	Pde4b	Rnf5	Tgoln1
Acot9	Cdh2	Eid1	Hoxa4	Lrrc59	Pdgfb	Rpa1	Thbs1
Acp5	Cdh5	Eif1a	Hoxa5	Lsm4	Pdk2	Rpl22l1	Thbs2
Acta1	Cdkn1a	Eif2s2	Hp	Ltbp4	Pdk4	Rps17	Thoc4
Actn1	Cdkn1c	Eif3c	Hs1bp3	Lyve1	Pecam1	Rps27l	Timp1
Adamts4	Cds2	Eif3e	Hs6st1	Macrod1	Pfn2	Rps6ka2	Timp3
Adm	Cdt1	Eif3j	Hsbp1	Maff	Pgd	Rrm1	Tinagl1
Adss	Cdv3	Eif5	Hsd17b12	Mafk	Pgk1	Rrm2	Tiparp
Afp	Cebpd	Eif6	Hsp90aa1	Mal	Phlda1	Rrs1	Tkt
Ahcyl2	Cenpe	Ell2	Hsp90ab1	Map2k6	Phldb1	Rsad2	Tle6
Aifm1	Ces3	Eln	Hspa1a	Map3k7ip3	Phlpp	Rtkn2	Tlk2
Akr1b8	Ch25h	Elovl7	Hspa1b	March5	Phxr4	Rtn2	Tm7sf3
Akr1c13	Chi3l1	Enc1	Hspa5	March7	Pi4k2b	Rwdd2b	Tmcc2
Aldh1a1	Chic2	Ensmusg00000040078	Hspa8	Mbd1	Pim1	S100a11	Tmem119
Aldh3a1	Chmp4b	Ensmusg00000050347	Hspa9	Mboat1	Pim3	S100a14	Tmem159
Aldoa	Chordc1	Epb4.1l5	Hspb1	Mcart1	Pitpnc1	S100a6	Tmem184a
Als2cr13	Chrnb1	Epha2	Hspb8	Mcee	Pkm2	S100a8	Tmem37
Amd-ps3	Churc1	Ercc6l	Hspd1	Mcm5	Pkp2	S100a9	Tmem45a
Ampd3	Cidea	Ereg	Hspe1	Mcm7	Pkp3	Samd8	Tmem49
Angptl4	Ckb	Errfi1	Hsph1	Med8	Pla1a	Sars	Tnc
Anks1	Cks1b	Esd	Id4	Meis1	Pla2g15	Sash1	Tnfrsf12a
Anln	Cldn3	Ext2	Idi1	Melk	Pla2g4a	Sc4mol	Tnfsf12
Anxa1	Cldn4	F3	Ier2	Men1	Plaa	Scamp1	Tnpo3
Anxa3	Cldn7	F7	Ifi202b	Mest	Plaur	Scd1	Tnrc6c
Anxa4	Clec16a	Fabp4	Ifi203	Mett11d1	Plcb3	Scel	Tob2
Anxa7	Clec4a2	Fam108a	Ifrd1	Mgat5	Plekhf1	Scp2	Topbp1
Anxa8	Clec4n	Fam134b	Igj	Mif	Plk3	Sdc1	Tor1b
Aox1	Clip4	Fam69b	Igsf5	Mmp11	Plod2	Sdc3	Tpi1
Apoc2	Clu	Fanca	Il1b	Mmp15	Plp2	Sdccag3	Tpm2
Arc	Clybl	Fasn	Il1r1	Mmp3	Plscr2	Sec61a1	Trak1
Arcn1	Col3a1	Fbln2	Il1r2	Mprip	Pmaip1	Sec62	Trdmt1
Areg	Col6a3	Fbxo4	Il33	Mpzl2	Pno1	Selm	Trf
Arf3	Cops3	Fcgrt	Impact	Mrpl16	Pnrc1	Sema3f	Trib3
Arg1	Coq7	Fdps	Incenp	Mrpl28	Podxl	Sephs2	Trim35
Arg2	Cotl1	Fgfbp1	Inmt	Mrpl30	Pomp	Sept2	Trip13
Arhgap21	Cpne1	Fgfr4	Ints6	Mrpl46	Pon3	Serpina1a	Trp53inp1

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Csf3r
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Ctps
Ctsh
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Ctsz
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Ccr1	Dusp16	Hbegf	Loc100047896	Obfc2a	Rabl4	Taldo1	Zfp281
Ccr2	E2f6	Hdac5	Loc100048076	Ogfrl1	Rad23b	Tapbp	Zfp292
Ccr5	Ebi3	Helz	Loc14210	Ogn	Ranbp1	Taz	Zfp36
Ccrn4l	Edem3	Hes6	Loc630729	Omd	Rarg	Tbc1d15	Zfp574
Cct3	Edn1	Hexb	Loc635418	Orf61	Rars	Tbca	Zfp90
Cct6a	Eef2k	Higd2a	Loc638798	Orm1	Rdh10	Tbx2	Zkscan1
Cd2ap	Efemp2	Hint1	Loc640441	Osgin1	Rfk	Tc2n	Zwint
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Table S3 The 755 proteins selected in the dataset GSE13268

Symbol	Symbol	Symbol	Symbol	Symbol	Symbol	Symbol	Symbol
Aanat	Cald1	Dnm1	Gss	LOC679958	Parm1	RGD1307682	Sppl2a
Abca3	Calr	Dnm2	Gsta3	LOC681004	Pax8	RGD1308059	Spry2
Abhd3	Caly	Dnm3	Gsta5	LOC682360	PCOLCE2	RGD1308117	Sptbn1
Acbd4	Cant1	Dpep1	Gstm2	LOC682469	Pdc	RGD1308448	Sra1
Acly	Capza1	Dpysl4	Gstm5	LOC682999	Pde1b	RGD1308772	Srpx
Acot2	Car5b	Dusp3	Gstm7	LOC685277	Pde3b	RGD1308782	Ssfa2
Acox1	Card9	Dync1h1	Gsto1	LOC685707	Pde6d	RGD1309350	Stk32c
Acpl2	Cars	Ebf1	Gsto2	LOC686774	Pdgfrl	RGD1309534	Stmn4
Acsf2	Cast	Ednrb	Gstp1	LOC687090	Pdhb	RGD1309540	Strn
Acsl4	Cbx3	Egfr	Gstt1	LOC688228	Pdhx	RGD1309651	Sts
Acsl5	Ccdc127	Egr1	Gstt2	LOC689147	Pdia3	RGD1309676	Sulf2
Acss2	Ccdc17	Ehd1	Gtf2i	LOC689329	Pdia6	RGD1310348	Sult1a1
Actr1a	Ccl24	Ehd2	Guk1	LOC691170	Pdlim2	RGD1310351	Svep1
Actr1b	Ccl9	Eif3d	Gys2	Loxl2	Pdzrn3	RGD1310587	Synj1
Adamts15	Ccna2	Eif5a2	Hbp1	Ltv1	Pfkfb3	RGD1559909	Synj2
Adcy4	Ccnb2	Eif5b	Hcca2	Lyplal1	Pgcp	RGD1560011	Tac1
Adfp	Ccnd2	Emilin2	Hcrtr2	Lztr1	Pgm5	RGD1562284	Tada1l
Adhfe1	Cd163	Enah	Hes3	Man1b1	Pgrmc1	RGD1562717	Tbata
Aga	Cd209g	Entpd4	Hist2h2aa3	Map2k1	Pias3	RGD1563422	Tbc1d9b
Agap2	Cd55	Epb4.1l2	Hist3h2a	Map2k2	Picalm	RGD1563684	Tbl1x
Agpat4	Cd5l	Epc2	Hmgcs2	Map4k4	Pigq	RGD1563863	Tcf25
Ahcyl2	Cd74	Ephx2	Hnrph1	Map7d1	Pik3r3	RGD1564228	Tcf7l2
Ahnak	Cd9	Erh	Homer2	Mbd3	Pim3	RGD1564541	Tect2
Aig1	Cd99	Ermp1	Hprt1	Mdfic	Pip5k1b	RGD1565002	Tes
Ak3	Cdc20	Esrra	Hpx	Me1	Pir	RGD1565432	Tex15
Ak3l1	Cdc5l	Etnk2	Hs2st1	Mecr	Pitpnb	Rgs7bp	Tgfb1i1
Akap12	Cdh13	Etv1	Hsd11b2	Med4	Pja2	Rhbdf1	Tgfbr3
Akr1b7	Cdk105	Fabp5	Hsd17b12	Meis2	Plbd1	Rmnd5b	Tgm2
Akt1	Cdr2	Fabp6	Hsd17b8	Meox2	Plcb1	Rraga	Tgoln1
Akt2	Cela1	Fah	Hsf2	Mettl6	Plce1	Rragc	Tinagl1
Aldh1a1	Cenpk	Faim	Hspa12a	Mfn2	Pld1	Rrm2	Tk1
Aldh1a2	Cep70	Fam103a1	Hspa4l	MGC109340	Pld2	Scand1	Tkt
Alg11	Ces3	Fam105a	Hspe1	MGC72955	Plekhg3	Scara5	Tmem120a
Anapc11	Cetn2	Fam107a	Ica1	MGC72974	Plin	Scd1	Tmem150c
Ang1	Cfp	Fam117b	Idh1	Mgll	Plp2	Scn7a	Tmem160
Angptl4	Cgref1	Fam171a1	Ifrd2	Mgmt	Plxna2	Scpep1	Tmem195
Ankrd52	Chpt1	Fat1	Ift20	Mgst2	Pmepa1	Sdf2	Tmem206
Ankrd6	Chrdl1	Fbln2	Igfbp3	Mipep	Pmm1	Sec62	Tmem208
Ano10	Chrna1	Fbn1	Igfbp6	Mki67	Pnpla3	Sel1l	Tmem43
Ano6	Cirbp	Fbxo23	Igsf1	Mmp2	Pola2	Selenbp1	Tmem45b
Anxa1	Clcn4-2	Fbxo4	Il13ra2	Mospd1	Pold2	Selm	Tmem50b
Anxa5	Clec10a	Fcrls	Il17re	Mpzl2	Polr1c	Senp6	Tmsbl1
Anxa6	Clec7a	Fdx1l	Il18bp	Mrp63	Pols	Sept8	Tnfaip1

Ap2a2
Ap2s1
Ap3m2
Apex1
Apln
Apln
Aplp1
Aplp2
Appl2
Arhgdib
Arhgef15
Arhgef18
Armc9
Armcx1
Asf1a
Asgr2
Asna1
Atf5
Atl2
Atp2b3
Atp4a
Atp4b
Atp6v0c
Atpif1
Atrn
Atxn2
Atxn2l
Avpr2
B3gntl1
B4galt5
B4galt6
Bace2
Basp1
Basp1
Bat2d1
Bckdhb
Bcl2l13
Blcap
Blnk
Bloc1s1
Bnip2
Brd7
Bre
Brms1l
Brp44l
Cltb
Cma1
Cmc1
Cmtm6
Cndp1
Cnih4
Cnksr2
Cnot1
Cnr1
Col15a1
Col4a1
Col4a2
Col5a2
Col5a3
Col8a1
Copb2
Cp
Cpeb1
Cpne8
Crebl2
Crebzf
Crim1
Crlf2
Crot
Csf2ra
Csgalnact1
Ctbp2
Cthrc1
Ctnnbip1
Ctnnbl1
Ctps2
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Ctsb
Ctsh
Ctsz
Cttn
Cul1
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Cyp11b1
Cyp4f5
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Dapk1
Dbil5
Dcakd
Ddc
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Fgfr1
Fgl2
Fhl1
Fitm2
Fkbp11
Fkbp1a
Fmo1
Fmo2
Fmo3
Fn1
Fndc1
Folr1
Foxn3
Frmd5
Frs2
Frzb
Fstl1
Ftsj3
Fxyd5
Fzd1
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Gbe1
Gbp2
Gcgr
Gdap2
Geft
Gfpt2
Gif
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Gja7
Glb1l2
Glrx1
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Gnai1
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Gnb2
Gnb3
Gnb5
Gng11
Golga3
Golsyn
Gpam
Gpc4
Gpld1
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Ipmk
Iscu
Isoc1
Itgam
Itgb2
Itgb5
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Kcnip1
Kcns3
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Kctd9
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Klhdc5
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Ldhb
Lef1
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Mrpl37
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Mxd4
Mxra8
Myeov2
N6amt2
Nanos3
Nck2
Ndufb3
Ndufc1
Neo1
Nfia
Nfkb1
Nfkbia
Nfyc
Nit1
Nkain3
Nkd1
Nkx3-1
Nlk
Nme1
Nnmt
Npdc1
Npr3
Nptn
Npy1r
Nr4a1
Nr4a2
Nr4a3
Nsg1
Nudt7
Nup37
Nxt1
Ocrl
Odf3b
Olah
Olfml3
Olr1
Omd
Orc5l
Ppap2c
Ppapdc1b
Ppie
Ppm1k
Ppp1cc
Ppp2r2b
Ppp4r2
Pqlc1
Prdx3
Prdx4
Prl6a1
Prom1
Prpsap2
Prss23
Psma4
Psma6
Psme2
Pter
Ptprm
Ptprr
Ptprz1
Purg
Pwwp2a
Pxdn
Pxk
Pygl
Rab13
Rab22a
Rab4a
Rab7l1
Rap1gap
Rapgef4
Rarres2
Rasal2
Rassf4
Rbm3
Rbms3
Rbmx
Rbp7
Rcan2
Rcn3
Rdh12
Recql
Reep5
Rem1
Serf1
Serpina12
Serpinb9
Serpinf1
Serpinh1
Setd3
Sft2d2
Sfxn1
Sgms1
Sh2d4a
Sh3bgrl
Sh3bgrl3
Sh3tc1
Shmt1
Siglec5
Slain2
Slc12a4
Slc17a5
Slc20a1
Slc25a1
Slc25a36
Slc2a3
Slc31a2
Slc35a1
Slc38a10
Slc38a7
Slc39a8
Slc41a2
Slc43a1
Slc43a2
Slc9a3
Slco2b1
Slco3a1
Slmap
Smarca1
Smarce1
Smoc2
Smpd2
Smpd3
Snx8
Snx9
Soat1
Sorbs2
Sox17
Sp1
Tp53i13
Trdmt1
Trhde
Trip10
Tshr
Tslp
Tsnax
Tspan12
Tspan9
Ttc1
Ttc25
Ttc27
Tubb3
Tubb5
Tusc4
Tusc5
Twsg1
Uap1l1
Uchl1
Ulk2
Unc93b1
Usf2
Usp39
Utp15
Utp3
Uxs1
Vamp1
Vkorc1l1
Vma21
Vps29
Wasl
Wbp2
Wbp5
Wdfy2
Wdr18
Wdr37
Xbp1
Xdh
Ykt6
Zadh2
Zbtb24
Zdhhc20
Zdhhc4
Zfp180
Zfp189

Brsk1
Btnl1
Bub3
Bysl
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C6
Cabin1
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Ddt
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Dlk1
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Papss2
Parg
Rft1
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RGD1307315
RGD1307396
Sparc
Spire1
Spire2
Spns2
Spop
Spp1
Zfp398
Zfp423
Zfp426l
Zfp469
Zh16
Zwilch

Table S4 Basic information of dynamic networks for the influenza H3N2 data (GSE30550)

GSE30550	number of nodes		number of edges	
	asymptomatic	symptomatic	asymptomatic	symptomatic
initial	2400	2400	16498	16498
0h	2093	2120	8519	9143
5h	2031	2139	7829	8932
12h	2017	2095	7166	8173
21h	2063	2132	7065	8749
29h	2066	2096	7769	8504
36h	1985	2161	6993	9325
45h	1965	2147	7169	10017
53h	2079	2183	7680	10498
60h	2048	2150	7908	10363
69h	2049	2047	6855	7995
77h	2062	2107	7693	8743
84h	2084	2080	7974	8661
93h	2011	2087	7320	8507
101h	1965	2042	7073	8264
108h	2114	2152	7688	8445

Table S5 Basic information of dynamic networks for the influenza H1N1 data (GSE52428)

GSE52428	number of nodes		number of edges	
	asymptomatic	symptomatic	asymptomatic	symptomatic
initial	2400	2400	16498	16498
0h	2037	2060	7911	8541
5h	1963	2019	6845	8113
12h	1967	2004	6874	7967
21h	1943	2025	7050	8436
29h	2004	2041	7562	8687
36h	1967	2094	7259	9677
45h	1991	2138	7297	10453
53h	1924	2172	6951	11409
60h	1960	2191	7388	11404
69h	2087	2083	8400	10119
77h	2005	2176	7778	11138
84h	2064	2082	7872	9877
93h	2013	2035	7918	9289
101h	1926	2022	6911	8474
108h	2023	2117	7250	8829

Table S6 Basic information of dynamic networks for the acute lung injury data (GSE2565)

GSE2565	**number of nodes**		**number of edges**	
	control	**case**	**control**	**case**
initial	770	770	5890	5890
0h	640	640	4586	4624
0.5h	640	638	4553	4586
1h	641	637	4504	4561
8h	638	639	4496	4521
12h	638	639	4489	4502
24h	640	636	4463	4492
48h	634	636	4427	4443
72h	637	639	4409	4433

Table S7 Basic information of dynamic networks for the type 2 diabetes mellitus data (GSE13268)

GSE13268	**number of nodes**		**number of edges**	
	control	**case**	**control**	**case**
initial	755	755	4054	4054
4w	624	623	2684	2799
8w	619	621	2407	2505
12w	624	625	2272	2366
16w	621	623	2124	2268
20w	620	624	2038	2176

Table S8 Protein modules appearing in each time point in the asymptomatic networks for the influenza H3N2 data (GSE30550)

	the proteins in module							
module 1	DDX58	HERC5	HERC6	IFI27	IFI35	IFI44	IFI44L	IFI6
	IFIH1	IFIT1	IFIT2	IFIT3	IRF7	IRF9	ISG15	MX1
	OAS1	OAS2	OAS3	OASL	RSAD2	XAF1	…	
module 2	CD19	CD22	CD72	CD79A	CD79B	IGHM	MS4A1	POU2AF1
module 3	PDS5B	RNGTT	PDS5A	STAG1				
module 4	DIS3	EXOSC2	EXOSC8	GTPBP1	SKIV2L2	ZFP36	SUPV3L1	
module 5	C14orf166	DDX1	RTCB					
module 6	TIMM10	TIMM22	TIMM9	TOMM20	TOMM70A			

Table S9 Protein modules appearing in each time point in the symptomatic networks for the influenza H3N2 data (GSE30550)

	the proteins in module							
module 1	ADAR	DDX58	DDX60	GBP1	GBP2	HERC6	IFI27	IFI35
	IFI44	IFI44L	IFI6	IFIH1	IFIT1	IFIT2	IFIT3	IFIT5
	IFITM1	IRF2	IRF7	IRF9	ISG15	ISG20	MX1	MX2
	OAS1	OAS2	OAS3	OASL	RSAD2	RTP4	XAF1	…
module 2	CD19	CD22	CD72	CD79A	CD79B	IGHM	MS4A1	POU2AF1
module 3	PDS5B	RNGTT	PDS5A	STAG1				
module 4	CDX4	NAP1L1	NAP1L2	NAP1L3	NAP1L4			
module 5	AZI1	CEP192	ALMS1	CEP57	CEP76	OFD1	PCNT	SFI1
	TUBGCP3	TUBGCP4	TUBGCP5					

Table S10 Protein modules appearing in each time point in the asymptomatic networks for the influenza H1N1 data (GSE52428)

	the proteins in module							
module 1	ADAR	DDX58	GBP1	GBP2	HERC6	IFI27	IFI35	IFI44
	IFI44L	IFI6	IFIH1	IFIT1	IFIT2	IFIT3	IFITM1	IRF1
	IRF2	IRF7	IRF9	ISG15	ISG20	MX1	MX2	OAS1
	OAS2	OAS3	OASL	RSAD2	RTP4	XAF1	…	
module 2	PDS5B	PDS5A	RNGTT	STAG1				

Table S11 Protein modules appeared in each time point in symptomatic networks for influenza H1N1 data (GSE52428)

	the proteins in module							
module 1	GBP1	GBP2	ADAR	IFI27	IFI35	IFI44	IFI44L	IFI6
	IFIH1	IFIT1	IFIT2	IFIT3	IFITM1	IRF1	IRF2	IRF7
	IRF9	ISG15	ISG20	MX1	MX2	OAS1	OAS2	OAS3
	OASL	RSAD2	RTP4	XAF1	…			
module 2	CDX4	NAP1L1	NAP1L2	NAP1L3	NAP1L4			

Table S12 Protein modules appearing in each time point in the asymptomatic networks for the acute lung injury data (GSE2565)

	the proteins in module							
module 1	Bnip3	Hk2	Aldoa	Ldha	Pgd	Pgk1	Pkm2	Slc2a1
	Taldo1	Tkt	Tpi1	Arhgef12	Pard6b	Prkci	Rhoj	Rhou
	Gtf2f2	Pcf11	Papolg	Ptbp1	U2af1			
module 2	Akr1b8	Aldh3a1	Gclc	Gclm	Gpx2	Gsr	Gsta1	Gsta2
	Gsta3	Gsta4	Loc100047868	Mafk	Nqo1	Sult1a1	Txnrd1	
module 3	Dnajc2	Dnajc21	Eif1a	Gnl3	Kti12	Nmd3	Nsun4	Rrs1
module 4	Cldn3	Cldn4	Cldn7	Kcnk1	Krt18	Krt19	Krt7	Krt8

Table S13 Protein modules appearing in each time point in the case networks for the acute lung injury data (GSE2565)

	the proteins in module							
module 1	Bnip3	Hk2	Aldoa	Ldha	Pgd	Pgk1	Pkm2	Slc2a1
	Taldo1	Tkt	Tpi1	Arhgef12	Pard6b	Prkci	Rhoj	Rhou
	Gtf2f2	Pcf11	Papolg	Ptbp1	U2af1			
module 2	Ensmusg00000050347	Lgals1	Lgals3	Plp2	S100a11	Anxa8	S100a6	
module 3	Akr1b8	Aldh3a1	Gclc	Gclm	Gpx2	Gsr	Gsta1	Gsta2
	Gsta3	Gsta4	Loc100047868	Mafk	Nqo1	Sult1a1	Txnrd1	
module 4	Actn1	Acta1	Spnb2	Tnc	Tpm2			

Table S14 Protein modules appearing in each time point in the control networks for the type 2 diabetes mellitus data (GSE13268)

	the proteins in module							
module 1	Akr1b7	Fmo1	Glrx1	Gpx7	Gss	Gsta3	Gstm2	Gstm5
	Gstm7	Gsto1	Gsto2	Gstp1	Gstt1	Gstt2	Me1	Mgst2
	Prdx3	Sult1a1	Xdh	Ankrd6	Frzb	Fzd1	Acpl2	Lef1
	Nkd1	Nlk	Sox17	C6	Ermp1	Ppap2c	Sgms1	Smpd2
	Smpd3	Cyp11a1	Cyp11b1	Fdx1l	Hsd11b2	Tmem50b		
module 2	Adcy4	Anxa1	Ccl9	Cnr1	Ednrb	Gcgr	Geft	Gnai1
	Gnb2	Gnb3	Gng11	Hcrtr2	Npy1r	Pik3r3	Plcb1	Tac1
module 3	Acox1	Acot2	Acsf2	Acsl4	Acsl5	Adfp	Angptl4	Fabp5
	Lyplal1	Mgll	Plin	Pnpla3	Scd1			

Table S15 Protein modules appearing in each time point in the case networks for the type 2 diabetes mellitus data (GSE13268)

	the proteins in module							
module 1	Akr1b7	Fmo1	Glrx1	Gpx7	Gss	Gsta3	Gstm2	Gstm5
	Gstm7	Gsto1	Gsto2	Gstp1	Gstt1	Gstt2	Me1	Mgst2
	Prdx3	Sult1a1	Xdh	Ankrd6	Frzb	Fzd1	Acpl2	Lef1
	Nkd1	Nlk	Sox17	C6	Ermp1	Ppap2c	Sgms1	Smpd2
	Smpd3	Cyp11a1	Cyp11b1	Fdx1l	Hsd11b2	Tmem50b		
module 2	Adcy4	Anxa1	Ccl9	Cnr1	Ednrb	Gcgr	Geft	Gnai1
	Gnb2	Gnb3	Gng11	Hcrtr2	Npy1r	Pik3r3	Plcb1	Tac1
module 3	Agpat4	Dgkz	Chpt1	Etnk2	Gpam	Gpld1	Pld1	Pld2
	Ppap2c							
module 4	Apex1	Ctnnbl1	Ddx19a	Erh	Ftsj3	Hspe1	Ltv1	Mrpl21
	Mrpl32	Mt1a	Nup37	Nxt1	Polr1c	Psma4	Psma6	Ttc27
	Utp15	Utp3	Wdr18					
module 5	Adamts15	Cela1	Fmo2	Pmm1	Serpina12			

Table S16 All protein modules appearing in each time point in both the asymptomatic and symptomatic networks for the influenza H3N2 data (GSE30550)

	the proteins in module							
module 1 **(HM1)**	DDX58	HERC5	HERC6	IFI27	IFI35	IFI44	IFI44L	IFI6
	IFIH1	IFIT1	IFIT2	IFIT3	IRF7	IRF9	ISG15	MX1
	OAS1	OAS2	OAS3	OASL	RSAD2	XAF1	…	
module 2	CD19	CD22	CD72	CD79A	CD79B	IGHM	MS4A1	POU2AF1
module 3	PDS5B	RNGTT	PDS5A	STAG1				

Table S17 All protein modules appearing in each time point in both the asymptomatic and symptomatic networks for the influenza H1N1 data (GSE52428)

	the proteins in module							
module 1 **(HM2)**	ADAR	DDX58	GBP1	GBP2	HERC6	IFI27	IFI35	IFI44
	IFI44L	IFI6	IFIH1	IFIT1	IFIT2	IFIT3	IFITM1	IRF1
	IRF2	IRF7	IRF9	ISG15	ISG20	MX1	MX2	OAS1
	OAS2	OAS3	OASL	RSAD2	RTP4	XAF1		

Table S18 All protein modules appearing in each time point in both the asymptomatic and symptomatic networks for the acute lung injury data (GSE2565)

	the proteins in module							
module 1 **(HM3)**	Bnip3	Hk2	Aldoa	Ldha	Pgd	Pgk1	Pkm2	Slc2a1
	Taldo1	Tkt	Tpi1	Arhgef12	Pard6b	Prkci	Rhoj	Rhou
	Gtf2f2	Pcf11	Papolg	Ptbp1	U2af1			
module 2	Akr1b8	Aldh3a1	Gclc	Gclm	Gpx2	Gsr	Gsta1	Gsta2
	Gsta3	Gsta4	Loc100047868	Mafk	Nqo1	Sult1a1	Txnrd1	

Table S19 All protein modules appearing in each time point in both the asymptomatic and symptomatic networks for the type 2 diabetes mellitus data (GSE13268)

	the proteins in module							
module 1 **(HM4)**	Akr1b7	Fmo1	Glrx1	Gpx7	Gss	Gsta3	Gstm2	Gstm5
	Gstm7	Gsto1	Gsto2	Gstp1	Gstt1	Gstt2	Me1	Mgst2
	Prdx3	Sult1a1	Xdh	Ankrd6	Frzb	Fzd1	Acpl2	Lef1
	Nkd1	Nlk	Sox17	C6	Ermp1	Ppap2c	Sgms1	Smpd2
	Smpd3	Cyp11a1	Cyp11b1	Fdx1l	Hsd11b2	Tmem50b		
module 2	Adcy4	Anxa1	Ccl9	Cnr1	Ednrb	Gcgr	Geft	Gnai1
	Gnb2	Gnb3	Gng11	Hcrtr2	Npy1r	Pik3r3	Plcb1	Tac1

Table S20 Descriptions of the HM1 of the influenza H3N2 data (GSE30550)

Symbol	Descriptions
IFIH1	interferon induced with helicase C domain 1
HERC6	hect domain and RLD 6
OAS3	2'-5'-oligoadenylate synthetase 3, 100kDa
HERC5	hect domain and RLD 5
RSAD2	radical S-adenosyl methionine domain containing 2
IFI44L	interferon-induced protein 44-like
IFI44	interferon-induced protein 44
OAS1	2',5'-oligoadenylate synthetase 1, 40/46kDa
OAS2	2'-5'-oligoadenylate synthetase 2, 69/71kDa
IFI35	interferon-induced protein 35
DDX58	DEAD (Asp-Glu-Ala-Asp) box polypeptide 58
IFIT3	interferon-induced protein with tetratricopeptide repeats 3
IRF9	interferon regulatory factor 9
IFIT2	interferon-induced protein with tetratricopeptide repeats 2
IFIT1	interferon-induced protein with tetratricopeptide repeats 1
IFI27	interferon, alpha-inducible protein 27
OASL	2'-5'-oligoadenylate synthetase-like
ISG15	ISG15 ubiquitin-like modifier
IRF7	interferon regulatory factor 7
XAF1	XIAP associated factor 1
MX1	myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse)
IFI6	interferon, alpha-inducible protein 6

Table S21 Descriptions of the HM2 of the influenza H1N1 data (GSE52428)

Symbol	Descriptions
IFIH1	interferon induced with helicase C domain 1
RTP4	receptor (chemosensory) transporter protein 4
IFITM1	interferon induced transmembrane protein 1 (9-27)
OAS3	2'-5'-oligoadenylate synthetase 3, 100kDa
RSAD2	radical S-adenosyl methionine domain containing 2
IFI44L	interferon-induced protein 44-like
OAS1	2',5'-oligoadenylate synthetase 1, 40/46kDa
OAS2	2'-5'-oligoadenylate synthetase 2, 69/71kDa
IFI35	interferon-induced protein 35
ISG20	interferon stimulated exonuclease gene 20kDa
ISG15	ISG15 ubiquitin-like modifier
XAF1	XIAP associated factor 1
MX1	myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse)
MX2	myxovirus (influenza virus) resistance 2 (mouse)
HERC6	hect domain and RLD 6
IFI44	interferon-induced protein 44
DDX58	DEAD (Asp-Glu-Ala-Asp) box polypeptide 58
IRF9	interferon regulatory factor 9
IFIT3	interferon-induced protein with tetratricopeptide repeats 3
IFIT2	interferon-induced protein with tetratricopeptide repeats 2
OASL	2'-5'-oligoadenylate synthetase-like
IFI27	interferon, alpha-inducible protein 27
IFIT1	interferon-induced protein with tetratricopeptide repeats 1
IRF7	interferon regulatory factor 7
IRF1	interferon regulatory factor 1
IRF2	interferon regulatory factor 2
IFI6	interferon, alpha-inducible protein 6
GBP2	guanylate binding protein 2, interferon-inducible
ADAR	adenosine deaminase, RNA-specific
GBP1	guanylate binding protein 1, interferon-inducible, 67kDa

Table S22 Descriptions of the HM3 of the acute lung injury data (GSE2565)

Symbol	Descriptions
Rhoj	ras homolog gene family, member J
Pkm2	predicted gene 6560; predicted gene 2124; predicted gene 6992; pyruvate kinase,muscle;similar to M2-type pyruvate kinase
U2af1	predicted gene 10232; predicted gene 6978; U2 small nuclear ribonucleoprotein auxiliary factor (U2AF) 1
Ptbp1	polypyrimidine tract binding protein 1; predicted gene 4900
Pgk1	phosphoglycerate kinase 1; predicted gene, EG668435
Rhou	ras homolog gene family, member U
Arhgef12	predicted gene 7281; predicted gene 5831; similar to SP140 nuclear body exchange factor (GEF) 12 protein (predicted);Rhoguanine nucle otide
Tkt	transketolase
Tpi1	triosephosphate isomerase 1; similar to triosephosphate isomerase 1
Gtf2f2	general transcription factor IIF, polypeptide 2
Pard6b	par-6 (partitioning defective 6) homolog beta (C. elegans)
Pcf11	cleavage and polyadenylation factor subunit homolog (S. cerevisiae)
Aldoa	aldolase A, fructose-bisphosphate; predicted gene 8767; predicted gene 7556
Taldo1	transaldolase 1
Prkci	protein kinase C, iota
Ldha	predicted gene 7997; lactate dehydrogenase A; predicted gene 5452
Bnip3	predicted gene 14506; BCL2/adenovirus E1B interacting protein 3; predicted gene 6532; similar to E1B 19K/B cl-2-binding protein homolog
Slc2a1	solute carrier family 2 (facilitated glucose transporter), member 1
Papolg	poly(A) polymerase gamma
Hk2	hexokinase 2
Pgd	phosphogluconate dehydrogenase

Table S23 Descriptions of the HM4 of the type 2 diabetes mellitus data (GSE13268)

Symbol	Descriptions
Fmo1	flavin containing monooxygenase 1
C6	complement component 6
Fdx1l	ferredoxin 1-like
Xdh	xanthine dehydrogenase
Gss	glutathione synthetase
Gstp1	glutathione-S-transferase, pi 1
Tmem50b	transmembrane protein 50B
Sgms1	sphingomyelin synthase 1
Gsta3	glutathione S-transferase A3
Nkd1	naked cuticle homolog 1 (Drosophila)
Mgst2	microsomal glutathione S-transferase 2
Sox17	SRY (sex determining region Y)-box 17
Gpx7	glutathione peroxidase 7
Cyp11b1	cytochrome P450, subfamily 11B, polypeptide 1
Gstt1	glutathione S-transferase theta 1
Gstt2	glutathione S-transferase, theta 2
Prdx3	peroxiredoxin 3
Lef1	lymphoid enhancer binding factor 1
Nlk	nemo like kinase
Frzb	frizzled-related protein
Gstm2	glutathione S-transferase mu 2
Ankrd6	ankyrin repeat domain 6
Ppap2c	phosphatidic acid phosphatase type 2c
Smpd3	sphingomyelin phosphodiesterase 3, neutral
Smpd2	sphingomyelin phosphodiesterase 2, neutral
Me1	malic enzyme 1, NADP(+)-dependent, cytosolic
Fzd1	frizzled homolog 1 (Drosophila)
Akr1b7	aldo-keto reductase family 1, member B7
Gsto2	glutathione S-transferase omega 2
Gsto1	glutathione S-transferase omega 1
Acpl2	acid phosphatase-like 2
Ermp1	endoplasmic reticulum metallopeptidase 1
Hsd11b2	hydroxysteroid 11-beta dehydrogenase 2
Cyp11a1	cytochrome P450, family 11, subfamily a, polypeptide 1
Glrx1	glutaredoxin 1 (thioltransferase)
Sult1a1	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 1
Gstm5	glutathione S-transferase, mu 5
Gstm7	glutathione S-transferase mu 3; glutathione S-transferase mu 4; glutathione S-transferase, mu 7

Table S24 Functional enrichment of GO biological processes in the identified DNB of the influenza H3N2 data (GSE30550)

Genes in DNB	GO Term	Description	P-Value
{DDX58,IRF9,IFIH1,ISG15,IRF7,RSAD2,IFI44,MX1,IFI35}	GO:0009615	response to virus	2.23E-13
{DDX58,IRF9,IFIH1,ISG15,IRF7,RSAD2,IFI44,MX1,IFI35}	GO:0051707	response to other organism	5.97E-10
{DDX58,IRF9,IFIH1,ISG15,IRF7,RSAD2,IFI44,MX1,IFI35}	GO:0009607	response to biotic stimulus	5.47E-09
{DDX58,IFIH1,OASL,OAS3,RSAD2,IFI44L,OAS1,OAS2,IFI6,IFI35}	GO:0006955	immune response	2.58E-08
{DDX58,IRF9,IFIH1,ISG15,IRF7,RSAD2,IFI44,MX1,IFI35}	GO:0051704	multi-organism process	4.65E-07
{DDX58,IFIH1,OASL,OAS3,RSAD2,IFI44L,OAS1,OAS2,IFI6,IFI35}	GO:0002376	immune system process	6.17E-07
{IFIH1,OAS3,RSAD2,IFI44L,IFI44,OAS1,OAS2,IFI35,DDX58,IRF9,OASL,ISG15,IRF7,MX1,IFI6}	GO:0050896	response to stimulus	1.02E-06

Table S25 Functional enrichment of GO biological processes in the identified DNB of the influenza H1N1 data (GSE52428)

Genes in DNB	GO Term	Description	P-Value
{DDX58,IRF9,IFIH1,ISG15,IRF7,RSAD2,IFI44,MX1,MX2,IFI35,ISG20}	GO:0009615	response to virus	1.45E-15
{DDX58,IRF9,IFIH1,IFITM1,ISG15,IRF7,RSAD2,IFI44, MX1,MX2,IFI35,ISG20}	GO:0009607	response to bioticstimulus	1.66E-11
{DDX58,IRF9,IFIH1,ISG15,IRF7,RSAD2,IFI44,MX1,MX2,IFI35,ISG20}	GO:0051707	response to other organism	2.86E-11
{DDX58,IFIH1,OASL,OAS3,RSAD2,IFI44L,OAS1,OAS2, GBP2,IFI6,IFI35,GBP1}	GO:0006955	immune response	8.37E-09
{IFIH1,RTP4,IFITM1,OAS3,RSAD2,IFI44L,IFI44,OAS1, OAS2,IFI35,ISG20,DDX58,IRF9,OASL,ISG15,IRF7,MX1,MX2,IFI6,GBP2,GBP1}	GO:0050896	response to stimulus	1.04E-08
{IFIH1,OAS3,RSAD2,IFI44L,OAS1,OAS2,IFI35,DDX58, OASL,IRF1,GBP2,IFI6, GBP1}	GO:0002376	immune system process	3.21E-08
{DDX58,IRF9,IFIH1,ISG15,IRF7,RSAD2,IFI44,MX1,MX2,IFI35,ISG20}	GO:0051704	multi-organism process	1.08E-07

Table S26 Functional enrichment of GO biological processes in the identified DNB of the acute lung injury data (GSE2565)

Genes in DNB	GO Term	Description	P-Value
{ALDOA,TPI1,LDHA,TALDO1,PKM2,PGD,HK2,TKT,PGK1}	GO:0006007	glucose catabolic process	6.14E-15
{ALDOA,TPI1,LDHA,TALDO1,PKM2,PGD,HK2,TKT,PGK1}	GO:0046365	monosaccharide catabolic process	8.22E-15
{ALDOA,TPI1,LDHA,TALDO1,PKM2,PGD,HK2,TKT,PGK1}	GO:0019320	hexose catabolic process	8.22E-15
{ALDOA,TPI1,LDHA,TALDO1,PKM2,PGD,HK2,TKT,PGK1}	GO:0046164	alcohol catabolic process	4.41E-14
{ALDOA,TPI1,LDHA,TALDO1,PKM2,PGD,HK2,TKT,PGK1}	GO:0044275	cellular carbohydrate catabolic process	4.41E-14
{ALDOA,TPI1,LDHA,TALDO1,PKM2,PGD,HK2,TKT,PGK1}	GO:0016052	carbohydrate catabolic process	5.70E-13
{ALDOA,TPI1,LDHA,TALDO1,PKM2,PGD,HK2,TKT,PGK1}	GO:0006006	glucose metabolic process	6.64E-11
{ALDOA,TPI1,LDHA,TALDO1,PKM2,PGD,HK2,TKT,PGK1}	GO:0019318	hexose metabolic process	2.08E-10
{ALDOA,TPI1,LDHA,TALDO1,PKM2,PGD,HK2,TKT,PGK1}	GO:0005996	monosaccharide metabolic process	5.64E-10
{ALDOA,TPI1,LDHA,PKM2,HK2,PGK1}	GO:0006096	glycolysis	4.69E-09
{TPI1,LDHA,TALDO1,PGD,TKT}	GO:0046496	nicotinamide nucleotide metabolic process	3.36E-07
{TPI1,LDHA,TALDO1,PGD,TKT}	GO:0006769	nicotinamide metabolic process	3.71E-07
{TPI1,LDHA,TALDO1,PGD,TKT}	GO:0019362	pyridine nucleotide metabolic process	4.09E-07
{TPI1,LDHA,TALDO1,PGD,TKT}	GO:0009820	alkaloid metabolic process	4.09E-07
{TPI1,TALDO1,PGD,TKT}	GO:0006098	pentose-phosphate shunt	4.54E-07
{TPI1,LDHA,TALDO1,PGD,TKT}	GO:0006733	oxidoreduction coenzyme metabolic process	8.90E-07
{TPI1,TALDO1,PGD,TKT}	GO:0006739	NADP metabolic process	1.25E-06
{TPI1,LDHA,TALDO1,PGD,TKT}	GO:0043603	cellular amide metabolic process	1.29E-06
{TPI1,LDHA,TALDO1,PGD,TKT}	GO:0019748	secondary metabolic process	8.47E-06
{TPI1,PGD,TKT,PGK1}	GO:0046364	monosaccharide biosynthetic process	1.76E-05
{ALDOA,TPI1,LDHA,PKM2,HK2,PGK1}	GO:0006091	generation of precursor metabolites and energy	1.97E-05
{TPI1,LDHA,PKM2,PGK1}	GO:0006090	pyruvate metabolic process	3.53E-05
{TPI1,PGD,TKT,PGK1}	GO:0046165	alcohol biosynthetic process	3.53E-05
{TPI1,LDHA,TALDO1,PGD,TKT}	GO:0006732	coenzyme metabolic process	7.82E-05
{TPI1,PGD,TKT,PGK1}	GO:0034637	cellular carbohydrate biosynthetic process	1.14E-04
{TALDO1,PGD,TKT}	GO:0019321	pentose metabolic process	1.88E-04
{TPI1,LDHA,TALDO1,PGD,TKT}	GO:0051186	cofactor metabolic process	1.93E-04
{TPI1,PGD,TKT,PGK1}	GO:0016051	carbohydrate biosynthetic process	3.63E-04

Table S27 Functional enrichment of GO biological processes in the identified DNB of the type 2 diabetes mellitus data (GSE13268)

Genes in DNB	GO Term	Description	P-Value
{GSTM2,GSTA3,SULT1A1,GSTP1,GSTM7}	GO:0006805	xenobiotic metabolic process	2.63E-07
{GSTM2,GSTA3,SULT1A1,GSTP1,GSTM7}	GO:0009410	response to xenobiotic stimulus	4.32E-07
{GSS,GSTA3,GSTT1,GSTT2,GSTP1}	GO:0006749	glutathione metabolic process	5.82E-07
{ME1,XDH,ERMP1,CYP11B1,C6,SGMS1,PRDX3,GSTM5,GLRX1, GSTM7,GSS,GSTM2,FMO1,SULT1A1,GSTO2,GSTO1,GSTA3, CYP11A1,NLK,LEF1,GSTT1,GSTT2,AKR1B7,HSD11B2,SMPD3, GSTP1,SMPD2}	GO:0008152	metabolic process	2.47E-06
{GSS,GSTA3,SULT1A1,GSTT1,GSTT2,GSTP1}	GO:0006790	sulfur metabolic process	5.40E-06
{GSS,GSTA3,GSTT1,GSTT2,GSTP1}	GO:0006518	peptide metabolic process	5.91E-06
{GSS,GSTA3,SULT1A1,GSTT1,GSTT2,GSTP1}	GO:0006575	cellular amino acid derivative metabolic process	4.21E-05
{ME1,XDH,AKR1B7,CYP11A1,FMO1,CYP11B1,HSD11B2,PRDX3,GLRX1}	GO:0055114	oxidation reduction	6.44E-05
{ME1,GSTM2,CYP11A1,SULT1A1,HSD11B2,LEF1,GSTT1,PRDX3,GSTM7, MGST2}	GO:0010033	response to organic substance	2.05E-04
{CYP11A1,CYP11B1,SULT1A1,HSD11B2}	GO:0034754	cellular hormone metabolic process	4.32E-04
{CYP11A1,CYP11B1,SULT1A1,HSD11B2,SMPD3}	GO:0010817	regulation of hormone levels	4.84E-04
{GSS,GSTA3,GSTT1,GSTT2,GSTP1}	GO:0006732	coenzyme metabolic process	5.20E-04

Table S28 Pearson correlation coefficient (PCC) between the expression values of S1PR1 and those proteins of interest in the innate immunity pathways in 9 symptomatic subjects infected by the H3N2 influenza virus strain

	Symptomatic (Sx) subjects								
	1	5	6	7	8	10	12	13	15
MDA5	-0.378	-0.786	-0.545	-0.735	-0.79	-0.686	-0.535	-0.523	-0.643
MAPK	-0.101	0.112	0.019	-0.024	-0.077	0.59	0.481	0.705	0.318
HERC6	0.015	-0.806	-0.622	-0.766	-0.746	-0.648	-0.377	-0.558	-0.534
HERC5	-0.344	-0.819	-0.607	-0.781	-0.852	-0.701	-0.646	-0.654	-0.618
RIG-I	-0.43	-0.807	-0.508	-0.721	-0.788	-0.727	-0.657	-0.569	-0.629
IFI44L	-0.045	-0.794	-0.619	-0.749	-0.837	-0.671	-0.442	-0.61	-0.561
OAS2	-0.121	-0.805	-0.719	-0.806	-0.809	-0.675	-0.563	-0.66	-0.606
RSAD2	-0.186	-0.801	-0.603	-0.772	-0.824	-0.706	-0.556	-0.646	-0.665
IRF7	-0.207	-0.844	-0.734	-0.781	-0.803	-0.689	-0.489	-0.653	-0.522
IFIT3	-0.271	-0.839	-0.616	-0.785	-0.865	-0.719	-0.576	-0.653	-0.626
OAS1	-0.112	-0.787	-0.653	-0.795	-0.824	-0.678	-0.522	-0.617	-0.579
OAS3	-0.222	-0.816	-0.732	-0.782	-0.817	-0.694	-0.544	-0.673	-0.58
IFI35	-0.38	-0.843	-0.772	-0.787	-0.763	-0.707	-0.665	-0.657	-0.592
IFI6	-0.133	-0.789	-0.835	-0.798	-0.782	-0.69	-0.63	-0.678	-0.566
IFI44	-0.084	-0.767	-0.627	-0.697	-0.803	-0.666	-0.463	-0.547	-0.574
MX1	-0.296	-0.831	-0.745	-0.772	-0.841	-0.696	-0.582	-0.7	-0.604
IFIT1	-0.264	-0.803	-0.558	-0.764	-0.839	-0.694	-0.599	-0.64	-0.684
XAF1	-0.127	-0.715	-0.559	-0.745	-0.812	-0.697	-0.45	-0.467	-0.528
TLR3	0.465	-0.433	0.094	-0.052	-0.352	-0.371	-0.526	-0.261	-0.427
TBK1	-0.322	-0.162	-0.35	-0.104	-0.594	-0.452	0.142	0.116	-0.022
ISG15	-0.084	-0.801	-0.658	-0.776	-0.795	-0.713	-0.451	-0.655	-0.634
IKKβ	0.763	0.662	0.187	0.709	0.751	0.663	0.943	0.939	0.836
IFIT2	-0.541	-0.838	-0.516	-0.768	-0.809	-0.724	-0.696	-0.605	-0.66
MyD88	-0.159	-0.841	-0.593	-0.743	-0.798	-0.7	-0.371	-0.35	-0.289
OASL	-0.271	-0.85	-0.628	-0.823	-0.842	-0.722	-0.623	-0.695	-0.665
IRF3	0.413	0.071	0.026	0.448	0.698	0.699	0.315	0.669	0.837
IRF9	-0.329	-0.84	-0.495	-0.765	-0.866	-0.664	-0.194	-0.603	-0.417
TNF-α	0.425	-0.646	-0.58	-0.492	-0.793	-0.218	-0.101	-0.202	0.125
IL6	-0.086	-0.494	-0.357	-0.231	0.089	0.192	-0.601	0.123	-0.469
IKKα	0.162	0.342	0.313	0.16	-0.452	-0.165	0.602	0.736	0.389
NFκB	0.339	-0.202	-0.326	0.347	-0.2	0.166	0.66	0.257	0.702
IFI27	0.566	-0.646	-0.388	-0.617	-0.662	-0.395	-0.125	-0.372	-0.283
IFN-γ	0.209	-0.216	0.15	0.234	0.02	-0.543	-0.64	-0.473	-0.185
IFN-α	-0.03	-0.512	-0.212	-0.777	0.22	-0.175	0.01	-0.56	-0.572
IKKε	0.85	-0.316	-0.231	0.179	0.196	0.29	-0.286	-0.029	0.377
IFN-β	0.075	-0.427	-0.239	-0.033	-0.135	-0.23	-0.697	-0.734	-0.345

Note: The identified DNBs are marked in red and bold. Proteins with significant differences of correlations between the symptomatic and asymptomatic subjects are labeled in green background. The results indicate that most of the DNBs exhibit significant differences in the distributions of correlations between the two different clinical outcomes (marked in red and green background).

Table S29 Pearson correlation coefficient (PCC) between the expression values of S1PR1 and those proteins of interest in the innate immunity pathways in 8 asymptomatic subjects infected by the H3N2 influenza virus strain

	Asymptomatic (Asx) subjects								
	2	3	4	9	11	14	16	17	**P-value**
MDA5	-0.215	0.611	0.134	0.616	0.71	0.245	0.444	-0.204	0.000082
MAPK	-0.431	-0.508	-0.609	-0.666	-0.513	-0.417	-0.724	-0.455	0.000082
HERC6	-0.181	0.27	0.104	0.741	0.745	0.48	0.482	0.328	0.000165
HERC5	-0.407	-0.032	-0.202	0.407	0.12	-0.105	-0.047	-0.531	0.000329
RIG-I	-0.513	0.363	0.253	0.43	0.534	0.001	-0.009	-0.453	0.000576
IFI44L	-0.44	0.37	0.017	0.485	0.444	0.237	0.124	-0.524	0.000576
OAS2	-0.513	-0.342	-0.399	0.113	0.44	-0.012	0.039	0.091	0.000576
RSAD2	-0.507	0.306	-0.223	-0.103	0.237	0.158	0.032	-0.439	0.000576
IRF7	-0.433	-0.216	-0.159	0.46	-0.234	0.318	0.128	-0.244	0.000987
IFIT3	-0.51	-0.33	-0.195	0.146	-0.281	-0.032	-0.316	-0.525	0.001563
OAS1	-0.54	-0.175	-0.255	0.771	0.345	-0.03	0.197	-0.38	0.001563
OAS3	-0.576	-0.359	-0.387	-0.001	0.042	-0.009	-0.017	-0.353	0.001563
IFI35	-0.58	-0.36	-0.372	0.444	-0.674	0.104	-0.069	-0.425	0.002468
IFI6	-0.494	0.212	-0.202	0.544	-0.284	0.051	-0.025	-0.659	0.002468
IFI44	-0.46	0.647	0.031	0.573	0.616	-0.105	0.237	-0.616	0.002468
MX1	-0.519	-0.61	-0.412	-0.006	-0.196	-0.218	-0.159	-0.327	0.002468
IFIT1	-0.487	0.371	-0.027	0.16	-0.038	-0.283	0.227	-0.705	0.005512
XAF1	-0.62	-0.193	-0.373	-0.03	0.618	0.028	0.121	-0.259	0.005512
TLR3	-0.032	0.424	0.204	0.446	0.415	0.427	0.423	0.747	0.005512
TBK1	-0.067	0.564	0.629	0.262	0.436	0.179	0.565	-0.321	0.005512
ISG15	-0.41	0.518	-0.095	0.514	-0.121	-0.152	0.141	-0.668	0.007898
IKKβ	0.02	0.006	0.086	0.153	0.866	0.312	0.066	0.357	0.007898
IFIT2	-0.721	-0.38	-0.567	-0.414	-0.598	-0.451	-0.328	-0.555	0.01522
MyD88	-0.207	-0.383	-0.387	0.048	-0.065	0.187	-0.61	-0.277	0.046401
OASL	-0.67	-0.717	-0.448	0.137	-0.696	-0.308	-0.165	-0.432	0.074455
IRF3	0.591	-0.348	0.006	0.253	-0.16	0.387	0.192	0.556	0.074455
IRF9	-0.525	-0.522	-0.257	0.376	-0.54	-0.176	-0.496	-0.357	0.113945
TNF-α	-0.426	-0.12	0.406	-0.206	-0.066	-0.007	0.428	-0.191	0.138791
IL6	0.082	0.101	0.569	-0.028	0.044	-0.097	-0.311	0.311	0.138791
IKKα	0.224	0.66	0.858	0.685	0.584	0.512	0.446	-0.159	0.138791
NFκB	0.119	-0.336	-0.438	-0.005	0.512	0.004	-0.102	0.104	0.199589
IFI27	0.148	-0.364	-0.098	-0.442	-0.59	-0.245	-0.196	-0.155	0.23587
IFN-γ	0.404	0.314	-0.106	0.351	-0.487	-0.782	0.367	-0.067	0.276594
IFN-α	0.013	-0.727	0.228	-0.222	-0.516	-0.312	0.078	0.215	0.423447
IKKε	0.803	0.201	0.05	0.123	0.28	-0.127	0.218	0.668	0.423447
IFN-β	0.038	-0.306	-0.352	-0.368	-0.627	0.023	-0.033	0.021	0.480708

Note: The identified DNBs are marked in red and bold. Proteins with significant differences of correlations between the symptomatic and asymptomatic subjects are labeled in green background. The results indicate that most of the DNBs exhibit significant differences in the distributions of correlations between the two different clinical outcomes (marked in red and green background, P-value < 0.05).

Table S30 Pearson correlation coefficient (PCC) between the expression values of S1PR1 and those proteins of interest in the innate immunity pathways in 12 symptomatic subjects infected by the H1N1 influenza virus strain

	Symptomatic (Sx) subjects											
	2	3	6	7	8	9	10	12	13	17	19	20
IRF7	-0.778	-0.338	-0.727	-0.787	-0.656	-0.44	-0.5	-0.779	-0.788	-0.555	-0.906	-0.833
RIG-I	-0.599	0.6	-0.667	-0.874	-0.567	-0.371	0.116	-0.863	-0.848	-0.429	-0.931	-0.837
TLR3	-0.342	0.21	-0.718	-0.028	-0.242	0.07	0.227	-0.409	-0.484	0.012	-0.318	-0.359
MDA5	-0.401	0.825	-0.661	-0.856	-0.55	-0.328	0.713	-0.831	-0.809	-0.392	-0.939	-0.809
IFI44	-0.501	0.21	-0.686	-0.607	-0.558	-0.386	0.111	-0.624	-0.719	-0.405	-0.884	-0.825
IFIT1	-0.524	0.267	-0.699	-0.779	-0.626	-0.384	0.082	-0.759	-0.72	-0.279	-0.869	-0.803
IFI44L	-0.668	0.137	-0.682	-0.608	-0.578	-0.376	0.221	-0.574	-0.701	-0.444	-0.875	-0.826
IFIT3	-0.686	0.049	-0.712	-0.762	-0.611	-0.373	-0.228	-0.71	-0.748	-0.445	-0.902	-0.824
RSAD2	-0.577	0.044	-0.699	-0.663	-0.566	-0.386	0.007	-0.663	-0.743	-0.421	-0.896	-0.828
IFI35	-0.769	-0.446	-0.769	-0.854	-0.669	-0.416	-0.532	-0.822	-0.859	-0.557	-0.933	-0.882
HERC5	-0.621	0.185	-0.703	-0.829	-0.6	-0.371	0.237	-0.813	-0.786	-0.429	-0.909	-0.827
MX1	-0.72	-0.013	-0.706	-0.784	-0.615	-0.395	-0.141	-0.716	-0.777	-0.453	-0.892	-0.819
HERC6	-0.683	0.452	-0.714	-0.788	-0.595	-0.418	0.679	-0.745	-0.767	-0.475	-0.919	-0.827
IFI6	-0.695	0.145	-0.699	-0.675	-0.571	-0.345	-0.296	-0.538	-0.79	-0.475	-0.895	-0.821
IKKβ	0.271	-0.079	-0.113	0.464	0.091	0.252	0.389	0.952	0.645	0.203	0.764	0.736
IFN-β	-0.309	-0.44	-0.409	-0.545	-0.265	0.107	-0.088	-0.438	0	-0.047	-0.108	-0.378
OAS1	-0.686	0.271	-0.691	-0.679	-0.573	-0.358	0.316	-0.692	-0.762	-0.456	-0.893	-0.837
OASL	-0.727	-0.183	-0.723	-0.842	-0.659	-0.411	-0.41	-0.798	-0.817	-0.469	-0.926	-0.854
ISG15	-0.726	-0.086	-0.716	-0.695	-0.599	-0.353	-0.059	-0.602	-0.75	-0.422	-0.894	-0.83
TNF-α	-0.385	-0.404	-0.505	-0.05	-0.104	-0.043	0.014	-0.815	-0.275	-0.515	-0.801	-0.552
OAS2	-0.687	0.265	-0.697	-0.708	-0.61	-0.411	0.463	-0.711	-0.823	-0.495	-0.904	-0.834
TBK1	0.348	0.336	-0.168	-0.518	-0.131	-0.112	0.363	-0.85	-0.684	0.045	-0.794	-0.582
IFIT2	-0.62	0.03	-0.719	-0.826	-0.632	-0.431	-0.262	-0.853	-0.849	-0.399	-0.902	-0.816
OAS3	-0.663	0.109	-0.694	-0.742	-0.601	-0.434	0.493	-0.689	-0.791	-0.471	-0.907	-0.836
IRF9	-0.789	-0.123	-0.693	-0.706	-0.682	-0.418	-0.367	-0.641	-0.794	-0.367	-0.82	-0.815
MAPK	0.071	-0.342	0.074	0.581	-0.094	0.273	-0.469	-0.462	-0.136	0.128	0.247	0.631
IRF3	-0.307	-0.716	0	0.555	0.163	0.366	-0.023	0.818	0.507	-0.047	-0.031	0.355
MyD88	-0.581	0.564	-0.783	-0.816	-0.583	-0.347	0.031	-0.901	-0.831	-0.593	-0.903	-0.798
XAF1	-0.627	0.075	-0.669	-0.702	-0.572	-0.363	0.399	-0.616	-0.72	-0.508	-0.906	-0.826
IKKα	0.439	0.857	0.645	0.432	0.373	0.059	0.126	-0.552	0.183	0.429	0.327	-0.09
NFκB	-0.352	-0.137	-0.383	-0.045	-0.257	0.312	0.477	-0.129	0.205	-0.246	0.334	0.461
IL6	-0.446	0.182	0.103	0.153	0.039	0.692	0.133	-0.29	-0.101	0.286	0.031	-0.434
IFN-γ	0.414	-0.144	-0.256	0.098	0.149	0.34	0.122	-0.551	0.047	0.449	0.211	-0.108
IFI27	0.495	-0.718	-0.463	0.211	-0.45	-0.338	-0.245	-0.162	-0.529	-0.241	-0.513	-0.738
IFN-α	-0.164	-0.003	-0.328	-0.053	-0.45	0.001	-0.194	-0.618	-0.206	-0.134	-0.228	-0.002
IKKε	-0.384	-0.146	-0.352	-0.061	-0.085	0.429	0.088	0.561	0.324	-0.393	-0.046	0.136

Note: The identified DNBs are marked in red and bold. Proteins with significant differences of correlations between the symptomatic and asymptomatic subjects are labeled in green background. The results indicate that most of the DNBs exhibit significant differences in the distributions of correlations between the two different clinical outcomes (marked in red and green background).

Table S31 Pearson correlation coefficient (PCC) between the expression values of S1PR1 and those proteins of interest in the innate immunity pathways in 11 asymptomatic subjects infected by the H1N1 influenza virus strain.

	Asymptomatic (Asx) subjects										
	1	4	5	11	14	15	16	18	21	22	23	**P-value**
IRF7	-0.451	-0.297	-0.35	-0.356	-0.331	-0.787	-0.232	-0.617	-0.323	-0.304	-0.232	0.003
RIG-I	0.689	0.169	-0.264	0.467	0.313	-0.821	-0.067	-0.565	0.103	-0.22	0.8	0.007
TLR3	-0.209	0.152	0.186	0.469	0.085	-0.147	0.019	0.093	0.098	0.441	0.288	0.009
MDA5	0.838	0.503	-0.271	0.599	0.456	-0.765	-0.292	-0.362	0.243	-0.064	0.91	0.011
IFI44	0.298	0.133	-0.211	-0.205	0.308	-0.688	-0.283	-0.391	-0.009	0.037	-0.104	0.013
IFIT1	0.426	0.252	-0.297	0.086	0.251	-0.711	-0.142	-0.394	-0.276	-0.232	-0.107	0.013
IFI44L	0.11	0.173	-0.311	-0.124	0.603	-0.695	-0.011	-0.511	0.327	-0.16	-0.067	0.015
IFIT3	0.117	0.159	-0.354	-0.648	0.088	-0.785	-0.116	-0.509	-0.356	-0.17	-0.043	0.015
RSAD2	0.052	-0.02	-0.266	-0.466	0.325	-0.749	-0.145	-0.496	0.249	-0.12	0.454	0.015
IFI35	-0.53	-0.323	-0.402	-0.686	-0.656	-0.839	-0.261	-0.641	-0.247	-0.616	0.279	0.018
HERC5	0.232	0.14	-0.337	-0.258	0.454	-0.777	-0.195	-0.542	-0.182	-0.485	-0.093	0.021
MX1	0.067	-0.049	-0.393	-0.573	0.126	-0.771	-0.328	-0.676	-0.172	-0.595	0.104	0.021
HERC6	0.581	0.015	-0.258	0.228	-0.452	-0.783	0.179	-0.473	-0.024	-0.299	0.479	0.025
IFI6	0.155	0.116	-0.437	-0.347	-0.501	-0.769	-0.279	-0.414	-0.094	-0.285	-0.445	0.025
IKKβ	0.44	0.258	-0.474	-0.155	-0.007	0.816	-0.587	-0.263	-0.188	-0.185	0.229	0.025
IFN-β	-0.131	0.179	0.446	0.036	-0.378	0.12	-0.074	0.246	-0.257	0.136	-0.392	0.029
OAS1	0.588	0.469	-0.221	-0.316	-0.045	-0.724	-0.489	-0.599	-0.202	-0.411	0.261	0.034
OASL	-0.306	-0.083	-0.417	-0.544	-0.139	-0.819	-0.276	-0.679	-0.606	-0.556	0.156	0.034
ISG15	-0.462	-0.136	-0.324	-0.402	-0.457	-0.765	0.157	-0.574	0.466	-0.414	0.202	0.039
TNF-α	-0.278	0.554	0.021	0.467	-0.109	-0.587	-0.005	-0.146	0.459	0.11	-0.519	0.045
OAS2	0.381	-0.129	-0.233	-0.543	0.259	-0.749	-0.379	-0.698	-0.262	-0.495	0.51	0.053
TBK1	0.208	0.394	-0.101	0.669	0.524	-0.438	-0.311	0.129	-0.034	0.318	-0.087	0.06
IFIT2	0.052	-0.09	-0.303	-0.827	0.237	-0.833	-0.631	-0.693	-0.273	-0.217	-0.029	0.069
OAS3	0.228	-0.16	-0.307	-0.573	0.224	-0.794	-0.566	-0.673	-0.431	-0.448	0.171	0.069
IRF9	-0.315	-0.251	-0.599	-0.664	-0.059	-0.759	-0.361	-0.665	-0.444	-0.718	0.083	0.079
MAPK	0.007	-0.378	-0.231	-0.791	0.084	-0.212	-0.661	-0.565	-0.438	-0.08	0.343	0.079
IRF3	0.006	-0.41	-0.284	-0.729	-0.633	0.64	0.318	-0.17	0.001	-0.671	-0.224	0.103
MyD88	0.258	0.007	-0.42	-0.381	-0.28	-0.889	-0.696	-0.679	-0.409	-0.296	0.238	0.103
XAF1	0.083	0.286	-0.187	-0.816	0.269	-0.733	-0.67	-0.66	0.109	0.123	0.607	0.148
IKKα	0.759	0.549	0.313	0.775	0.542	0.164	-0.004	0.444	0.192	0.567	0.605	0.186
NFκB	-0.12	-0.213	-0.242	-0.646	-0.065	-0.103	-0.303	-0.558	-0.123	-0.529	0.503	0.23
IL6	0.145	0.091	0.267	0.01	0.107	0.431	0.417	0.244	0.413	-0.602	-0.33	0.406
IFN-γ	-0.113	0.091	0.259	-0.159	-0.256	-0.009	-0.202	0.467	-0.343	0.322	0.068	0.479
IFI27	-0.007	-0.342	-0.377	-0.943	-0.401	-0.571	0.298	-0.302	0.012	0.148	-0.182	0.518
IFN-α	-0.306	-0.753	0.099	-0.365	0.015	0.137	-0.044	-0.054	0.036	-0.3	-0.548	0.644
IKKε	-0.383	-0.015	0.222	0.114	-0.303	-0.536	0.48	-0.221	-0.02	-0.556	0.358	0.735

Note: The identified DNBs are marked in red and bold. Proteins with significant differences of correlations between the symptomatic and asymptomatic subjects are labeled in green background. The results indicate that most of the DNBs exhibit significant differences in the distributions of correlations between the two different clinical outcomes (marked in red and green background, P-value < 0.05).

Supplementary MATLAB source codes

****

Remark: We list two important M files for constructing the dynamic networks. The detailed MATLAB source codes are available at: http://maths.whu.edu.cn/teach/lj/?title=xfzou, or, http://maths.whu.edu.cn/d/file/shizililiang/lj/2015-01-26/a35859758c8cc953516fb2edfe73f732.pdf. If the readers are interested in all the source data and codes in this paper, they can contact with Prof. Xiufen Zou: xfzou@whu.edu.cn. We can provide all the executable M files.

****

Function LP_OP.m

```
% Function LP_OP.m: the optimization problem is transformed into a standard linear programming
% (LP) problem.
function [J,f1]=LP_OP(Y,X,lamda1,lamda2,beta)
%Y is the expression value of target gene
%X is the expression values of genes interact with target gene
%lamda1 is the regularization parameter for guarantee the sparseness
%lamda2 is the regularization parameter for guarantee the continuity
%beta is a priori information about interactions
%J is the strength of interaction relations
%f1 is the optimization of objective function values
[n,m]=size(Y);%Y is a row vector, n=1,m is the number of samples
[p,q]=size(X);%X is a matrix, p is the number of genes, q is the number of samples
c=n*m;
h=n*p;
f=[ones(1,2*c),lamda1*ones(1,2*h),lamda2*ones(1,2*h)]';
%f is a column vector, the first 2c lines are u, v coefficient, after 2h lines
%are ksai, yeta coefficient
A1=sparse(1:c,1:c,ones(1,c),c,c);
A2=sparse(1:c,1:c,-ones(1,c),c,c);
Z=X';%a line is a sample, a column is a gene
Z_1=1/2*Z;
Y_1=Y';%Y_1 is a column vector
beq=Y_1-Z_1*beta;
beq=[beq;beta];
Z_2=-Z_1;
Aeq1=full([A1,A2,Z_1,Z_2,Z_1,Z_2]);
B=zeros(p,c);
B_1=sparse(1:p,1:p,ones(1,p),p,p);
B_2=sparse(1:p,1:p,-ones(1,p),p,p);
Aeq2=[B,B,full(B_1),full(B_2),full(B_2),full(B_1)];
Aeq=[Aeq1;Aeq2];
Aeq=sparse(Aeq);
clear A1 A2 Z_1 Z_2 Z Y_1;
lb=zeros(2*(c+h+h),1);
[x,f1]=linprog(f,[],[],Aeq,beq,lb);
```

```
x=x';
s=sparse(n,p);
t=sparse(n,p);
s1=sparse(n,p);
t1=sparse(n,p);
J=sparse(n,p);
J1=sparse(n,p);
    for k=1:p
        s(1,k)=x(2*m+k);
        t(1,k)=x(2*m+p+k);
        s1(1,k)=x(2*m+2*p+k);
        t1(1,k)=x(2*m+3*p+k);
    end
J=s-t;
J=full(J);
end
```

Function ODE.m

```
% Function ode_net.m: Inferring dynamic strength matrices of control(asymptomatic) and
%case(symptomatic) samples
function [As_ode_net,S_ode_net]=ode_net(lamda1,lamda2,nt,na,ns)
  %lamda1 is the regularization parameter for guarantee the sparseness
  %lamda2 is the regularization parameter for guarantee the continuity
  %nt is the number of time points
  %na is the number of control(asymptomatic) samples
  %ns is the number of case(symptomatic) samples
  %As_ode_net is a cell array of strength matrices of control(asymptomatic)
  %S_ode_net is a cell array of strength matrices of case(symptomatic)
  load As_cen_diff.mat;%gene second-order central difference expression of control(asymptomatic)
  load S_cen_diff.mat;%gene second-order central difference expression of case(symptomatic)
  load As_adj.mat;%the simplified control(asymptomatic) network based on MI
  load S_adj.mat;%the simplified case(symptomatic) network based on MI
  load data_GC.mat;%sequence of gene expression data
  [m,~]=size(data_GC);
  % construction asymptomatic(control) dynamic network
  As_ode_net{1}=As_adj{1};
  for t=1:nt-1
      As_ode_net{t+1}=zeros(m,m);
      A=As_adj{t};
      X=[];
      for i=1:m
          for s=1:na
             Y(i,s)=As_cen_diff{s}(i,t);
          end
          k=0;
          for j=1:m
              if A(i,j)==1
```

```
                k=k+1;
                X(k,:)=data_CG(j,1+t:nt:na*nt);
                beta(k,1)=As_ode_net{t}(i,j);
            end
        end
        if k~=0
            [J,f1]=LP_OP(Y(i,:),X,lamda1,lamda2,beta);
            k=0;
            for j=1:m
                if A(i,j)==1
                    k=k+1;
                    As_ode_net{t+1}(i,j)=J(k);
                end
            end
            X=[];
            beta=[];
        end
    end
end
save As_ode_net.mat As_ode_net;
%% construction symptomatic(case) dynamic network
S_ode_net{1}=S_adj{1};
for t=1:nt-1
    S_ode_net{t+1}=zeros(m,m);
    A=S_adj{t};
    X=[];
    for i=1:m
        for s=1:ns
            Y(i,s)=S_cen_diff{s}(i,t);
        end
        k=0;
        for j=1:m
            if A(i,j)==1
                k=k+1;
                X(k,:)=data_CG(j,na*nt+1+t: nt:(ns+na)*nt);
                beta(k,1)=S_ode_net{t}(i,j);
            end
        end
        if k~=0
            [J,f1]=LP_OP(Y(i,:),X,lamda1,lamda2,beta);
            k=0;
            for j=1:m
                if A(i,j)==1
                    k=k+1;
                    S_ode_net{t+1}(i,j)=J(k);
                end
            end
```

```
                X=[];
                beta=[];
            end
        end
    end
    save S_ode_net.mat S_ode_net;
```