

Supplementary Materials

Using Multi-objective Optimization to Identify Dynamical Network Biomarkers as Early-warning Signals of Complex Diseases

Fatemeh Vafaei^{1,2}

¹Charles Perkins Centre, University of Sydney, Sydney, Australia

²School of Mathematics and Statistics, University of Sydney, Sydney, Australia

fatemeh.vafaei@sydney.edu.au

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Supplementary Texts

Permutation test to assess the significance of a DNB's signal intensity

In order to assess the significance of the elevation of a DNB composite index at the pre-disease time, a permutation test has been conducted for each of the compared methods. The test statistic is $\Delta I = I_t - I_{t-1}$, where t is the pre-disease time. For a DNB of size n predicted by a compared algorithm, the distribution of the test statistic under the null hypothesis is obtained by randomly generating a group of n genes from the gene pool (i.e., the set of all differentially expressed genes), and repeating this process for 1000 times. The test statistic is then computed for each of the "random DNBs" using the pre-disease time as predicted by the compared algorithm. The p-value is estimated as the fraction of random DNBs whose test statistic is equal or higher than the ΔI of the DNB of the compared algorithm.

Supplementary Figures

Figure S1

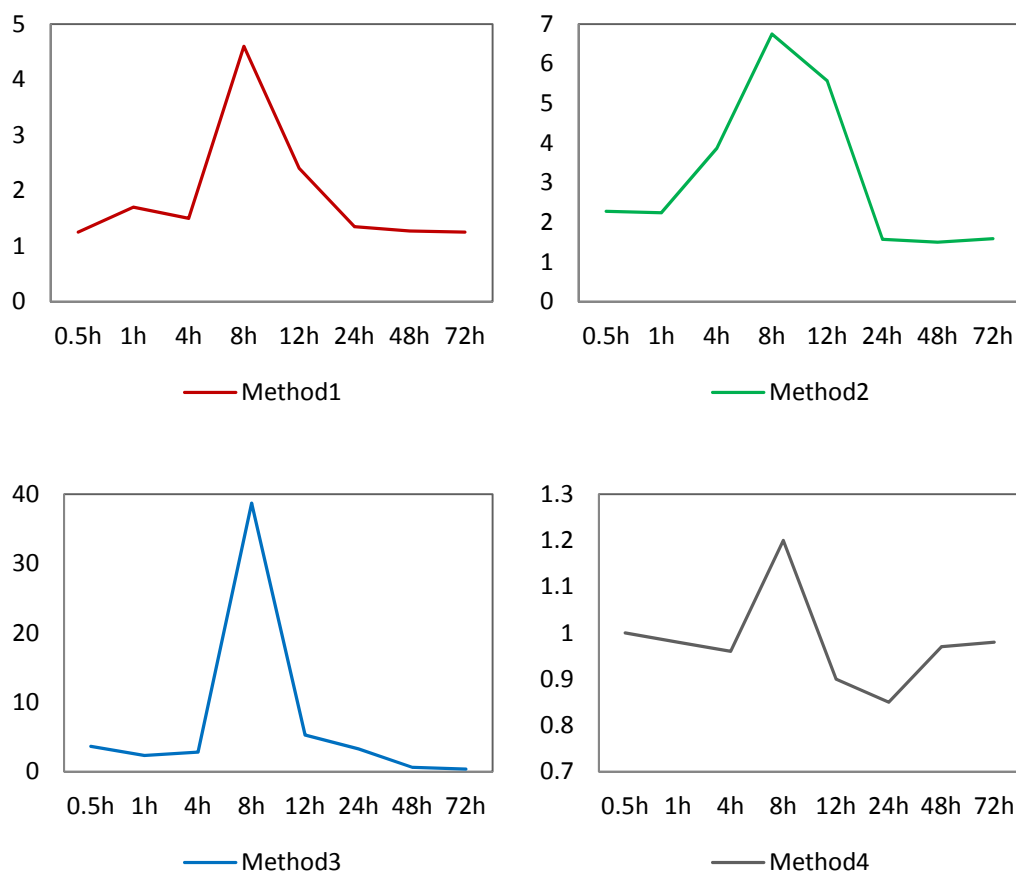


Figure S1: Temporal behaviors of DNBs predicted by different methods in terms of the change of the corresponding composite indices over time; Method 1: [Chen *et al*, 2012], Method 2: [Yu *et al*, 2013], Method 3: [Zeng *et al*, 2014], Method 4: [Li *et al*, 2015]. Information for Method 1 and Method 4 were extracted from the original papers. Method 3 has provided the java source code of the proposed algorithm. The code was run on acute lung injury (ALI) data, and the identified modules were extracted for consequent analysis. Method 2 was reproduced for ALI database.

Figure S2

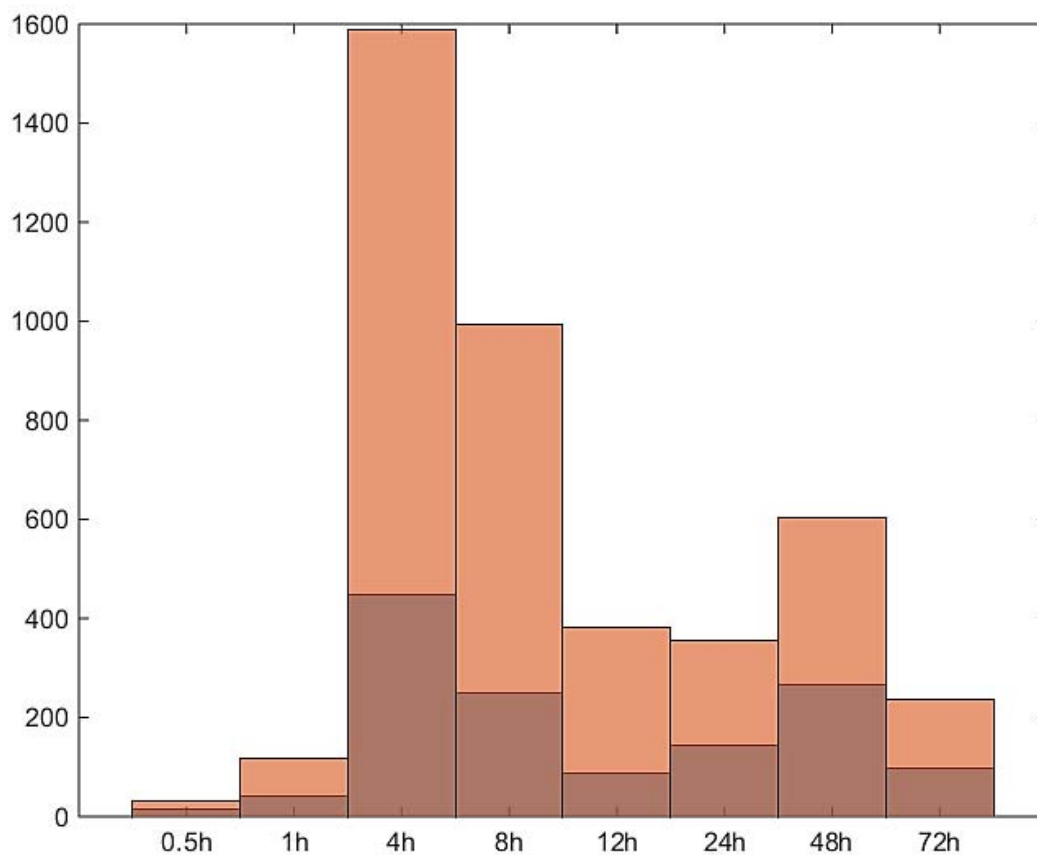


Figure S2: Distribution of genes deregulated at different time-points. Each bar of the histogram shows the number of genes whose deregulation commenced at the corresponding time. The significance is assessed according to the FDR q-value and the threshold is set to **0.05** in pale orange histogram and to **0.01** in dark orange histogram.

Supplementary Tables

Table S1

Table S1: List of 89 genes included in the extended DNB (EDNB).

Genes in Extended DNB			
ALDH3A1	ECT2	LGALS1	SHISA2
ANLN	EGR1	LGALS3	SLC4A1
APLNR	ERCC6L	LTF	SNCA
ASF1B	FCER1G	MAD2L1	SOCS3
AURKA	FKBP5	MCM5	SPAG5
BID	FOS	MELK	SPC25
BIRC5	GADD45G	MKI67	STEAP3
CCNB1	HELLS	MYC	STIL
CCNB2	HMGB2	NCAPG2	TACC3
CCNF	HSP90AA1	NUF2	TGFBI
CDC20	HSPA1B	PBK	TK1
CDCA5	HSPA8	PLK1	TK1
CDK1	HSPA9	PMAIP1	TNXB
CDKN2C	HSPB1	PRC1	TOP2A
CENPA	HSPD1	RACGAP1	TOP2A
CEP55	HSPH1	RAD51	TPX2
CHST15	JUN	RRM2	TRIP13
CKS1B	KIF20A	RTP3	TTN
CKS2	KIF23	S100A4	TUBA4A
CLEC2D	KRT18	S100A8	UBE2C
COL6A3	KRT8	S100A9	UHRF1
CTSK	LCN2	SHCBP1	XDH, and ZBTB16

Table S2**Table S2: List of 293 target genes (TGs) of the extended DNB significantly deregulated after time 4h.**

TGs de-regulated in t>4h (FDR p-value <0.05)						
ABCA1	CHRN1	FUT1	LZTR1	NID1	PSMD3	SRF
ABCB10	CLN3	FXR1	MAFF	NME1	PSMD5	SRI
ABCB6	CLU	GADD45A	MAGOH	NPM1	PTGER2	SRM
ACE	CNPY2	GALC	MAN2A1	NQO1	PTGES3	SRPR
ACTR3	CNTN1	GAPDH	MAPRE2	NR1D1	PTGS2	STOM
ACYP2	COL1A1	GCLC	MBD1	NR3C1	PTOV1	SYN2
ADCY9	COL5A1	GCLM	MCCC2	NRF1	PTP4A1	TBXA2R
ADRB1	COPS2	GDF15	MCL1	NTHL1	PTPN6	TFF1
ALDH9A1	COPS3	GJA1	MCM3	ODC1	PTPRF	TGFB1
ALDOA	COX7A2L	GSS	MDM2	PA2G4	RARA	TGFB2
AMD1	CR2	GSTO1	ME1	PCF11	RARB	TGFB3
AMPD3	CRADD	HBEGF	MEIS1	PCMT1	RBM3	TGM1
APP	CSTB	HERPUD1	MEN1	PCNA	RBM8A	THBS1
AREG	CXCR4	HEY1	MFNG	PDE6D	RFC2	TIMP1
ARF4	CYR61	HIF1A	MGEA5	PDGFA	RFX5	TIMP2
ASCL2	DBI	HMOX1	MGST1	PDGFB	RGS2	TNC
ATF3	DBP	HNRNPA1	MKKN1	PDGFRB	RNF4	TOMM20
ATF4	DDIT3	HNRPDL	MMP14	PKD2	RPL10	TOP1
ATP1A2	DDX1	HOXA5	MMP15	PECAM1	RPL15	TPR
ATP2A2	DGCR6	HOXB2	MMP19	PKM2	RPS6KA2	TRIM25
BAZ1B	DLEU2	HSD11B2	MMP2	PLA2G4A	SARS	TSC2
BCL2	DPYSL3	HSPA1A	MMP3	PLAT	SARS2	TSHB
BCL3	E2F1	HSPA8	MMP8	PLAUR	SCNN1B	TYK2
BID	EAPP	HSPD1	MSN	PLCB3	SEC23B	U2AF1
BMP4	EDN1	HSPE1	MSR1	PMAIP1	SERPINE1	UBA52
BRD7	EGR1	IER2	MTCH1	PMVK	SERPINE2	UBE2D3
CAPZA1	EIF2S1	IFNAR1	MUC1	POLA2	SFTPA1	UBE2G2
CBS	EIF4A1	IFRD2	MUC5B	POLE3	SFTPD	UCHL1
CBX5	EIF4E	ING1	MYB	PON1	SIRT1	USO1
CCL2	ESD	ISG20	MYC	POR	SLC20A1	USP11
CCRL2	ETF1	ITGA2	MYCL1	PPARG	SLC31A1	VAPA
CCT5	ETS1	ITGA5	MYCT1	PPP2CA	SLC39A8	VASP
CCT7	ETS2	JUN	NAB2	PRDX3	SLC3A2	VCAM1
CCT8	F3	JUNB	NAP1L1	PRDX6	SLC9A3R2	VCP
CD14	FABP4	KLK1B4	NCBP2	PREP	SMAD4	VEGFA
CD82	FANCA	LAIR1	NCL	PRKCSH	SNRPB	VHL
CD9	FASN	LAMA4	NDRG1	PRKDC	SOD2	VIM
CDKN1A	FGFR4	LAMP1	NDUFB5	PSAP	SPAST	WDR36
CDKN2B	FLT1	LAMP2	NFAT5	PSMA1	SPIB	XDH
CEBPB	FOS	LDLR	NFE2L1	PSMA5	SPINT1	ZFP36
CEBPD	FOSL1	LHB	NFIL3	PSMB5	SPP1	ZFP36L2
CEBPZ	FUS	LMNA	NFKBIL1	PSMD14	SQSTM1	

Table S3

Table S3: List of 61 genes in DisGeNet related to acute lung injury. Those genes which are among the deregulated TGs of the extended DNB are colored in red.

Genes related to acute lung injury in DisGeNet		
ACVR1	GSTM1	NOS2
ADRA2A	GSTP1	P2RY12
AGER	GSTT1	PECAM1
ALB	ICAM1	PLA2G2A
APOA1	IFNG	PLAU
ASCL1	IL10	PPARG
CAT	IL13	PTGS2
CCL2	IL18	SCGB1A1
CCL4L1	IL1B	SERPINE1
CXCL3	IL1RL1	SOD3
CXCL6	IL1RN	TFF1
CYP1A1	IL2	TFF2
EDN1	IL6	TGFB1
EPHX2	ITGB2	TIRAP
F2	KDR	TLR4
FAS	MMP7	TNF
FASLG	MST1R	TXN
FCGR1A	MTHFR	VEGFA
FCGR2B	MYLK	VIP
GJA1	NFE2L2	
GSR	NOD2	

Table S4**Table S4: GO terms (corrected p-value < 0.01) enriched by the extended DNB using BiNGO tool.**

GO-ID	corrected p-value	Description	Genes in test set
51301	8.68E-29	cell division	CKS1B, PRC1, AURKA, ANLN, CEP55, ZBTB16, SPC25, NCAPG2, TOP2A, CDCA5, HELLS, ERCC6L, CDK1, CCNF, TPX2, NUF2, BIRC5, CDC20, UBE2C, RACGAP1, MCM5, CCNB1, CCNB2, MAD2L1, PLK1, SPAG5
7049	7.83E-28	cell cycle	STEAP3, CKS1B, PRC1, AURKA, ANLN, CEP55, SPC25, CDKN2C, NCAPG2, CDCA5, HELLS, ERCC6L, TRIP13, CDK1, MKI67, CCNF, TPX2, NUF2, CDC20, BIRC5, RACGAP1, UBE2C, TACC3, RAD51, CCNB1, UHRF1, CCNB2, MAD2L1, PLK1, SPAG5, CKS2
279	8.16E-28	M phase	CDK1, MKI67, CCNF, NUF2, TPX2, CDC20, BIRC5, AURKA, ANLN, CEP55, TACC3, UBE2C, RAD51, CCNB1, SPC25, CCNB2, MAD2L1, PLK1, NCAPG2, SPAG5, CKS2, CDCA5, HELLS, TRIP13, ERCC6L
22403	1.32E-26	cell cycle phase	CDK1, MKI67, CCNF, NUF2, TPX2, CDC20, BIRC5, AURKA, ANLN, CEP55, TACC3, UBE2C, RAD51, CCNB1, SPC25, CCNB2, MAD2L1, PLK1, NCAPG2, SPAG5, CKS2, CDCA5, HELLS, TRIP13, ERCC6L
9987	3.93E-26	cellular process	STEAP3, PRC1, SNCA, S100A9, AURKA, PMAIP1, TTN, HSPH1, FOS, CDKN2C, TGFBI, LTF, SLC4A1, TOP2A, MYC, CDCA5, EGR1, CDK1, HSP90AA1, SOCS3, CCNF, TPX2, PBK, TACC3, UBE2C, ECT2, MCM5, RAD51, UHRF1, KRT18, MAD2L1, SPAG5, JUN, RRM2, GADD45G, TUBA4A, MELK, BID, XDH, CKS1B, HMGB2, FKBP5, ANLN, HSPA1B, CEP55, ZBTB16, ALDH3A1, TK1, SPC25, CENPA, NCAPG2, KRT8, FCER1G, ASF1B, HELLS, HSPA8, TRIP13, ERCC6L, HSPA9, TNXB, MKI67, LGALS3, LGALS1, NUF2, CDC20, BIRC5, RACGAP1, CCNB1, LCN2, CCNB2, PLK1, CKS2, HSPD1, KIF20A
6996	2.43E-25	organelle organization	BID, HMGB2, S100A9, SNCA, AURKA, ANLN, PMAIP1, HSPA1B, CEP55, TTN, SPC25, NCAPG2, CENPA, KRT8, ASF1B, TOP2A, MYC, CDCA5, HELLS, ERCC6L, CDK1, CCNF, NUF2, TPX2, CDC20, BIRC5, TACC3, UBE2C, CCNB1, CCNB2, MAD2L1, PLK1, SPAG5, JUN
22402	4.75E-25	cell cycle process	CDK1, MKI67, CCNF, NUF2, TPX2, CDC20, BIRC5, AURKA, ANLN, CEP55, TACC3, UBE2C, RAD51, CCNB1, SPC25, CCNB2, MAD2L1, PLK1, NCAPG2, SPAG5, CKS2, CDCA5, HELLS, TRIP13, ERCC6L
16043	6.19E-25	cellular component organization	BID, HMGB2, S100A9, SNCA, AURKA, ANLN, CEP55, PMAIP1, HSPA1B, TTN, SPC25, CENPA, NCAPG2, KRT8, TGFBI, FCER1G, ASF1B, TOP2A, MYC, CDCA5, HELLS, ERCC6L, CDK1, TNXB, LGALS3, CCNF, NUF2, TPX2, CDC20, BIRC5, TACC3, UBE2C, ECT2, CCNB1, LCN2, CCNB2, MAD2L1, PLK1, SPAG5, JUN, RRM2, TUBA4A
280	6.95E-24	nuclear division	CDK1, CCNF, NUF2, TPX2, CDC20, BIRC5, AURKA, ANLN, CEP55, UBE2C, CCNB1, SPC25, CCNB2, MAD2L1, PLK1, SPAG5, NCAPG2, CDCA5, HELLS, ERCC6L
7067	6.95E-24	mitosis	CDK1, CCNF, NUF2, TPX2, CDC20, BIRC5, AURKA, ANLN, CEP55, UBE2C, CCNB1, SPC25, CCNB2, MAD2L1, PLK1, SPAG5, NCAPG2, CDCA5, HELLS, ERCC6L
87	7.03E-24	M phase of mitotic cell cycle	CDK1, CCNF, NUF2, TPX2, CDC20, BIRC5, AURKA, ANLN, CEP55, UBE2C, CCNB1, SPC25, CCNB2, MAD2L1, PLK1, SPAG5, NCAPG2, CDCA5, HELLS, ERCC6L
48285	8.86E-24	organelle fission	CDK1, CCNF, NUF2, TPX2, CDC20, BIRC5, AURKA, ANLN, CEP55, UBE2C, CCNB1, SPC25, CCNB2, MAD2L1, PLK1, SPAG5, NCAPG2, CDCA5, HELLS, ERCC6L
278	3.68E-22	mitotic cell cycle	CDK1, CCNF, NUF2, TPX2, CDC20, BIRC5, AURKA, ANLN, CEP55, UBE2C, CCNB1, SPC25, CCNB2, MAD2L1, PLK1, SPAG5, NCAPG2, CDCA5, HELLS, ERCC6L
48522	2.20E-10	positive regulation of cellular process	BID, STEAP3, EGR1, CDK1, HMGB2, HSP90AA1, SOCS3, LGALS1, SNCA, TPX2, CDC20, BIRC5, ZBTB16, PMAIP1, ALDH3A1, RAD51, CCNB1, LCN2, FOS, RRM2, JUN, FCER1G, HSPD1, MYC, TOP2A
32502	2.77E-10	developmental process	XDH, STIL, HMGB2, ZBTB16, TTN, FOS, SHISA2, NCAPG2, KRT8, TOP2A, MYC, HELLS, TRIP13, EGR1, CDK1, HSP90AA1, LGALS3, SOCS3, LGALS1, CCNF, TPX2, CDC20, BIRC5, RACGAP1, TACC3, ECT2, RAD51, CCNB1, UHRF1, CCNB2, JUN, GADD45G
48518	4.06E-10	positive regulation of biological process	STEAP3, BID, HMGB2, SNCA, PMAIP1, HSPA1B, ZBTB16, ALDH3A1, FOS, FCER1G, TOP2A, MYC, EGR1, CDK1, HSP90AA1, SOCS3, LGALS1, TPX2, BIRC5, CDC20, RAD51, CCNB1, LCN2, JUN, RRM2, HSPD1
65007	4.06E-10	biological regulation	STEAP3, STIL, SNCA, S100A9, PMAIP1, FOS, CDKN2C, LTF, MYC, TOP2A, EGR1, CDK1, HSP90AA1, SOCS3, TPX2, UBE2C, TACC3, ECT2, MCM5, RAD51, CTSK, UHRF1, MAD2L1, KRT18, JUN, RRM2, GADD45G, BID, XDH, HMGB2, HSPA1B, ZBTB16, ALDH3A1, APLNR, KRT8, CLEC2D, FCER1G, ASF1B, HSPA8, HELLS, TNXB, LGALS1, NUF2, BIRC5, CDC20, RACGAP1, LCN2, CCNB1, CCNB2, HSPD1
7275	1.25E-09	multicellular organismal development	XDH, STIL, HMGB2, ZBTB16, TTN, FOS, SHISA2, NCAPG2, KRT8, TOP2A, MYC, HELLS, EGR1, CDK1, HSP90AA1, LGALS3, SOCS3, LGALS1, CCNF, TPX2, CDC20, BIRC5, RACGAP1, TACC3, RAD51, CCNB1, UHRF1, CCNB2, JUN, GADD45G

Table continues to the next page.

GO-ID	corrected p-value	Description	Genes in test set
48856	2.27E-09	anatomical structure development	XDH, STIL, HMGB2, ZBTB16, TTN, FOS, NCAPG2, KRT8, MYC, HELLS, TRIP13, EGR1, CDK1, HSP90AA1, LGALS3, SOCS3, LGALS1, CCNF, TPX2, CDC20, RACGAP1, TACC3, ECT2, RAD51, CCNB1, CCNB2, JUN, GADD45G
50794	9.76E-09	regulation of cellular process	XDH, BID, STEAP3, STIL, HMGB2, S100A9, SNCA, ZBTB16, HSPA1B, PMAIP1, ALDH3A1, APLNR, FOS, CDKN2C, KRT8, CLEC2D, FCER1G, ASF1B, TOP2A, MYC, HELLS, HSPA8, EGR1, CDK1, TNXB, HSP90AA1, SOCS3, LGALS1, TPX2, CDC20, BIRC5, RACGAP1, TACC3, ECT2, MCM5, RAD51, CCNB1, LCN2, UHRF1, KRT18, MAD2L1, JUN, RRM2, GADD45G, HSPD1
50896	1.01E-08	response to stimulus	XDH, HMGB2, S100A8, S100A9, SNCA, PMAIP1, HSPA1B, ALDH3A1, FOS, HSPH1, KRT8, CLEC2D, FCER1G, MYC, HSPA8, TRIP13, HSPA9, EGR1, CDK1, HSP90AA1, TACC3, RAD51, LCN2, UHRF1, JUN, GADD45G, HSPB1, HSPD1
50789	1.20E-08	regulation of biological process	XDH, BID, STEAP3, STIL, HMGB2, S100A9, SNCA, ZBTB16, HSPA1B, PMAIP1, ALDH3A1, APLNR, FOS, CDKN2C, KRT8, CLEC2D, FCER1G, ASF1B, TOP2A, MYC, HELLS, HSPA8, EGR1, CDK1, TNXB, HSP90AA1, SOCS3, LGALS1, TPX2, CDC20, BIRC5, RACGAP1, TACC3, UBE2C, ECT2, MCM5, RAD51, CCNB1, LCN2, UHRF1, KRT18, MAD2L1, JUN, RRM2, GADD45G, HSPD1
6950	1.31E-08	response to stress	CDK1, HSP90AA1, SNCA, PMAIP1, HSPA1B, TACC3, RAD51, ALDH3A1, LCN2, HSPH1, UHRF1, JUN, KRT8, CLEC2D, FCER1G, HSPB1, HSPD1, HSPA8, TRIP13, HSPA9
42981	1.91E-07	regulation of apoptosis	STEAP3, BID, STIL, SNCA, BIRC5, PMAIP1, HSPA1B, ZBTB16, RAD51, JUN, FCER1G, HSPD1, MYC, HELLS
43067	2.19E-07	regulation of programmed cell death	STEAP3, BID, STIL, SNCA, BIRC5, PMAIP1, HSPA1B, ZBTB16, RAD51, JUN, FCER1G, HSPD1, MYC, HELLS
10941	2.71E-07	regulation of cell death	STEAP3, BID, STIL, SNCA, BIRC5, PMAIP1, HSPA1B, ZBTB16, RAD51, JUN, FCER1G, HSPD1, MYC, HELLS
22607	2.76E-07	cellular component assembly	CDK1, TNXB, TPX2, TTN, CCNB1, LCN2, CENPA, RRM2, KRT8, TUBA4A, ASF1B, MYC, HELLS
32501	3.53E-07	multicellular organismal process	XDH, STIL, HMGB2, SNCA, ZBTB16, TTN, FOS, APLNR, SHISA2, NCAPG2, KRT8, TOP2A, MYC, HELLS, TRIP13, EGR1, CDK1, TNXB, HSP90AA1, LGALS3, SOCS3, LGALS1, CCNF, TPX2, CDC20, BIRC5, RACGAP1, TACC3, RAD51, CCNB1, UHRF1, CTSK, CCNB2, JUN, GADD45G
42221	4.31E-07	response to chemical stimulus	EGR1, XDH, CDK1, HMGB2, HSP90AA1, S100A8, SNCA, S100A9, HSPA1B, ALDH3A1, LCN2, FOS, JUN, KRT8, FCER1G, HSPD1, MYC
51716	4.33E-07	cellular response to stimulus	EGR1, CDK1, SNCA, S100A9, PMAIP1, HSPA1B, RAD51, LCN2, FOS, UHRF1, JUN, FCER1G, MYC, TRIP13
48523	7.58E-07	negative regulation of cellular process	EGR1, STIL, SOCS3, LGALS1, SNCA, BIRC5, PMAIP1, HSPA1B, ZBTB16, RAD51, CCNB1, MAD2L1, CDKN2C, JUN, CLEC2D, FCER1G, HSPD1, MYC, HELLS
48731	8.69E-07	system development	XDH, EGR1, STIL, CDK1, HMGB2, HSP90AA1, LGALS3, SOCS3, LGALS1, CCNF, CDC20, ZBTB16, RACGAP1, TTN, TACC3, RAD51, FOS, CCNB2, JUN, KRT8, GADD45G, MYC, HELLS
48519	8.79E-07	negative regulation of biological process	EGR1, STIL, SOCS3, LGALS1, SNCA, BIRC5, ZBTB16, PMAIP1, HSPA1B, TACC3, RAD51, CCNB1, MAD2L1, CDKN2C, JUN, CLEC2D, FCER1G, HSPD1, MYC, HELLS
51726	1.05E-06	regulation of cell cycle	CDK1, MAD2L1, JUN, GADD45G, TPX2, BIRC5, TACC3, MYC, HSPA8
44085	1.48E-06	cellular component biogenesis	CDK1, TNXB, TPX2, TTN, CCNB1, LCN2, CENPA, RRM2, KRT8, TUBA4A, ASF1B, MYC, HELLS
6323	1.81E-06	DNA packaging	CDK1, CENPA, NCAPG2, ASF1B, TOP2A, HELLS
48869	2.42E-06	cellular developmental process	EGR1, HMGB2, HSP90AA1, LGALS3, SOCS3, LGALS1, TPX2, CDC20, ZBTB16, RACGAP1, TTN, TACC3, ECT2, RAD51, CCNB1, JUN, KRT8, GADD45G, HELLS, TRIP13
9790	2.77E-06	embryonic development	CCNB1, STIL, CCNB2, NCAPG2, SOCS3, KRT8, BIRC5, ZBTB16, RACGAP1, TTN, TOP2A, MYC, RAD51
71103	3.74E-06	DNA conformation change	CDK1, CENPA, NCAPG2, ASF1B, TOP2A, HELLS
6259	5.03E-06	DNA metabolic process	UHRF1, RRM2, HSPA1B, TOP2A, MYC, HELLS, MCM5, TRIP13, TK1, RAD51
43066	6.41E-06	negative regulation of apoptosis	STIL, SNCA, FCER1G, BIRC5, HSPD1, HSPA1B, MYC, HELLS, RAD51
1836	6.93E-06	release of cytochrome c from mitochondria	BID, JUN, PMAIP1, MYC
43069	6.93E-06	negative regulation of programmed cell death	STIL, SNCA, FCER1G, BIRC5, HSPD1, HSPA1B, MYC, HELLS, RAD51

Table continues to the next page.

GO-ID	corrected p-value	Description	Genes in test set
30154	6.93E-06	cell differentiation	EGR1, HMGB2, HSP90AA1, LGALS3, SOCS3, LGALS1, TPX2, CDC20, ZBTB16, RACGAP1, TTN, TACC3, RAD51, CCNB1, JUN, GADD45G, KRT8, HELLS, TRIP13
51789	7.98E-06	response to protein stimulus	EGR1, FOS, HSP90AA1, HSPD1, HSPA1B, MYC
60548	8.60E-06	negative regulation of cell death	STIL, SNCA, FCER1G, BIRC5, HSPD1, HSPA1B, MYC, HELLS, RAD51
51239	9.55E-06	regulation of multicellular organismal process	EGR1, XDH, CDK1, HSP90AA1, LGALS1, SNCA, CDC20, HSPA1B, RAD51, CCNB1, JUN, CLEC2D, FCER1G, HSPD1, MYC
6915	2.63E-05	apoptosis	BID, STEAP3, KRT18, JUN, KRT8, GADD45G, TPX2, BIRC5, PMAIP1, MYC
8637	2.66E-05	apoptotic mitochondrial changes	BID, JUN, PMAIP1, MYC
6457	2.79E-05	protein folding	HSPH1, HSP90AA1, FKBP5, HSPD1, HSPA8, HSPA9
12501	2.88E-05	programmed cell death	BID, STEAP3, KRT18, JUN, KRT8, GADD45G, TPX2, BIRC5, PMAIP1, MYC
1701	3.76E-05	in utero embryonic development	CCNB1, STIL, CCNB2, NCAPG2, SOCS3, KRT8, TTN, RAD51
65003	3.76E-05	macromolecular complex assembly	CCNB1, LCN2, CDK1, CENPA, RRM2, TUBA4A, ASF1B, MYC, HELLS
44260	4.68E-05	cellular macromolecule metabolic process	FKBP5, AURKA, HSPA1B, TK1, FOS, HSPH1, ASF1B, TOP2A, MYC, HSPA8, HELLS, TRIP13, HSPA9, EGR1, CDK1, HSP90AA1, PBK, UBE2C, MCM5, RAD51, CCNB1, UHRF1, PLK1, JUN, RRM2, GADD45G, HSPD1, MELK
43170	4.92E-05	macromolecule metabolic process	FKBP5, AURKA, HSPA1B, TK1, FOS, HSPH1, ASF1B, TOP2A, MYC, HSPA8, HELLS, TRIP13, HSPA9, EGR1, CDK1, TNXB, HSP90AA1, PBK, UBE2C, MCM5, RAD51, CCNB1, UHRF1, CTSK, PLK1, JUN, RRM2, GADD45G, HSPD1, MELK
8219	5.83E-05	cell death	BID, STEAP3, KRT18, JUN, KRT8, GADD45G, TPX2, BIRC5, PMAIP1, MYC
43933	6.34E-05	macromolecular complex subunit organization	CCNB1, LCN2, CDK1, CENPA, RRM2, TUBA4A, ASF1B, MYC, HELLS
16265	6.77E-05	death	BID, STEAP3, KRT18, JUN, KRT8, GADD45G, TPX2, BIRC5, PMAIP1, MYC
33554	8.99E-05	cellular response to stress	LCN2, CDK1, UHRF1, JUN, SNCA, HSPA1B, PMAIP1, TRIP13, RAD51
51128	9.70E-05	regulation of cellular component organization	CCNB1, LCN2, MAD2L1, HSP90AA1, LGALS1, S100A9, TPX2, FCER1G, CDC20
51085	1.30E-04	chaperone mediated protein folding requiring cofactor	HSPH1, HSPD1, HSPA8
7005	1.55E-04	mitochondrion organization	BID, JUN, SNCA, PMAIP1, MYC
61077	1.60E-04	chaperone-mediated protein folding	HSPH1, HSPD1, HSPA8
7017	1.65E-04	microtubule-based process	NUF2, TPX2, TUBA4A, BIRC5, TACC3, KIF20A
51276	1.67E-04	chromosome organization	CDK1, MAD2L1, CENPA, NCAPG2, HSPA1B, ASF1B, TOP2A, HELLS
7126	1.67E-04	meiosis	MKI67, PLK1, CKS2, TRIP13, RAD51
51327	1.67E-04	M phase of meiotic cell cycle	MKI67, PLK1, CKS2, TRIP13, RAD51
51321	1.73E-04	meiotic cell cycle	MKI67, PLK1, CKS2, TRIP13, RAD51
6458	1.79E-04	'de novo' protein folding	HSPH1, HSPD1, HSPA8
51084	1.79E-04	'de novo' posttranslational protein folding	HSPH1, HSPD1, HSPA8
6916	1.83E-04	anti-apoptosis	BIRC5, HSPD1, HSPA1B, MYC, HELLS
7059	2.26E-04	chromosome segregation	MAD2L1, NUF2, BIRC5, TOP2A
7281	2.44E-04	germ cell development	CCNB1, HMGB2, TPX2, ZBTB16, TRIP13

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GO-ID	corrected p-value	Description	Genes in test set
50793	2.44E-04	regulation of developmental process	CCNB1, XDH, CDK1, HSP90AA1, SOCS3, LGALS1, JUN, CLEC2D, CDC20, MYC, RAD51
30261	2.49E-04	chromosome condensation	CDK1, NCAPG2, TOP2A
44237	2.57E-04	cellular metabolic process	XDH, FKBP5, SNCA, AURKA, HSPA1B, ALDH3A1, TK1, FOS, HSPH1, ASF1B, TOP2A, MYC, HELLS, HSPA8, TRIP13, HSPA9, EGR1, CDK1, TNXB, HSP90AA1, PBK, UBE2C, MCM5, RAD51, CCNB1, UHRF1, PLK1, JUN, RRM2, GADD45G, HSPD1, MELK
43523	2.80E-04	regulation of neuron apoptosis	JUN, SNCA, BIRC5, PMAIP1, RAD51
910	2.87E-04	cytokinesis	PRC1, PLK1, ANLN
19222	2.94E-04	regulation of metabolic process	EGR1, CDK1, HMGB2, TNXB, HSP90AA1, SOCS3, SNCA, S100A9, TPX2, ZBTB16, UBE2C, MCM5, CCNB1, LCN2, FOS, UHRF1, JUN, GADD45G, ASF1B, MYC, TOP2A, HELLS
42127	3.20E-04	regulation of cell proliferation	CCNB1, CDK1, CDKN2C, RRM2, JUN, CDC20, ZBTB16, PMAIP1, MYC, ALDH3A1
10033	3.25E-04	response to organic substance	EGR1, CDK1, FOS, HMGB2, HSP90AA1, SNCA, HSPD1, HSPA1B, MYC, ALDH3A1
42493	3.25E-04	response to drug	LCN2, FOS, JUN, SNCA, ALDH3A1
7010	3.34E-04	cytoskeleton organization	KRT8, S100A9, NUF2, TPX2, BIRC5, TACC3, TTN
60255	3.40E-04	regulation of macromolecule metabolic process	EGR1, CDK1, HMGB2, TNXB, SOCS3, SNCA, S100A9, TPX2, ZBTB16, UBE2C, MCM5, CCNB1, LCN2, FOS, UHRF1, JUN, ASF1B, MYC, TOP2A, HELLS
7006	3.66E-04	mitochondrial membrane organization	BID, SNCA, PMAIP1
44238	5.16E-04	primary metabolic process	XDH, FKBP5, SNCA, AURKA, HSPA1B, TK1, FOS, HSPH1, ASF1B, TOP2A, MYC, HELLS, HSPA8, TRIP13, HSPA9, EGR1, CDK1, TNXB, HSP90AA1, PBK, UBE2C, MCM5, RAD51, CCNB1, UHRF1, CTSK, PLK1, JUN, RRM2, GADD45G, HSPD1, MELK
43009	6.02E-04	chordate embryonic development	CCNB1, STIL, CCNB2, NCAPG2, SOCS3, KRT8, TTN, RAD51
8152	6.02E-04	metabolic process	STEAP3, XDH, FKBP5, SNCA, AURKA, HSPA1B, TK1, ALDH3A1, FOS, HSPH1, LTF, ASF1B, TOP2A, MYC, HELLS, HSPA8, TRIP13, HSPA9, EGR1, CDK1, TNXB, HSP90AA1, PBK, UBE2C, MCM5, RAD51, CCNB1, UHRF1, CTSK, PLK1, JUN, RRM2, GADD45G, HSPD1, MELK
9792	6.38E-04	embryonic development ending in birth or egg hatching	CCNB1, STIL, CCNB2, NCAPG2, SOCS3, KRT8, TTN, RAD51
9893	7.81E-04	positive regulation of metabolic process	CCNB1, LCN2, EGR1, CDK1, FOS, HMGB2, HSP90AA1, JUN, TPX2, TOP2A, MYC
45321	8.03E-04	leukocyte activation	EGR1, GADD45G, SNCA, FCER1G, HSPD1, HELLS
51094	1.01E-03	positive regulation of developmental process	CCNB1, CDK1, HSP90AA1, SOCS3, JUN, MYC, RAD51
48513	1.04E-03	organ development	EGR1, XDH, STIL, CDK1, HMGB2, SOCS3, CCNF, TTN, TACC3, CCNB2, JUN, KRT8, GADD45G, MYC, HELLS
8283	1.22E-03	cell proliferation	UHRF1, MKI67, NCAPG2, RACGAP1, TACC3, HELLS
2682	1.29E-03	regulation of immune system process	HSP90AA1, JUN, SNCA, CLEC2D, FCER1G, HSPD1, HSPA1B
70887	1.30E-03	cellular response to chemical stimulus	LCN2, EGR1, S100A9, SNCA, FCER1G, MYC
1775	1.32E-03	cell activation	EGR1, GADD45G, SNCA, FCER1G, HSPD1, HELLS
226	1.35E-03	microtubule cytoskeleton organization	NUF2, TPX2, BIRC5, TACC3
51240	1.37E-03	positive regulation of multicellular organismal process	CCNB1, CDK1, SNCA, FCER1G, HSPD1, MYC
10604	1.44E-03	positive regulation of macromolecule metabolic process	CCNB1, LCN2, EGR1, CDK1, FOS, HMGB2, JUN, TPX2, TOP2A, MYC
51173	1.49E-03	positive regulation of nitrogen compound metabolic process	CCNB1, EGR1, CDK1, FOS, HMGB2, HSP90AA1, JUN, TOP2A, MYC

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GO-ID	corrected p-value	Description	Genes in test set
7346	1.49E-03	regulation of mitotic cell cycle	CDK1, MAD2L1, TPX2, MYC
8284	1.49E-03	positive regulation of cell proliferation	CCNB1, CDK1, RRM2, JUN, CDC20, MYC, ALDH3A1
1933	1.53E-03	negative regulation of protein amino acid phosphorylation	CCNB1, JUN, SNCA
9628	1.53E-03	response to abiotic stimulus	KRT8, HSPB1, HSPA1B, PMAIP1, MYC, RAD51
1932	1.72E-03	regulation of protein amino acid phosphorylation	CCNB1, TNXB, SOCS3, JUN, SNCA
31325	1.72E-03	positive regulation of cellular metabolic process	CCNB1, EGR1, CDK1, FOS, HMGB2, HSP90AA1, JUN, TPX2, TOP2A, MYC
43065	1.92E-03	positive regulation of apoptosis	BID, STEAP3, JUN, ZBTB16, PMAIP1, MYC
45595	1.98E-03	regulation of cell differentiation	XDH, HSP90AA1, SOCS3, LGALS1, JUN, CLEC2D, CDC20, RAD51
43068	1.99E-03	positive regulation of programmed cell death	BID, STEAP3, JUN, ZBTB16, PMAIP1, MYC
7127	1.99E-03	meiosis I	CKS2, TRIP13, RAD51
2376	1.99E-03	immune system process	EGR1, CCNB2, GADD45G, S100A9, SNCA, FCER1G, HSPD1, TACC3, HELLS
6974	2.05E-03	response to DNA damage stimulus	CDK1, UHRF1, HSPA1B, PMAIP1, TRIP13, RAD51
31328	2.06E-03	positive regulation of cellular biosynthetic process	EGR1, CDK1, FOS, HMGB2, HSP90AA1, JUN, TPX2, TOP2A, MYC
48610	2.11E-03	reproductive cellular process	CCNB1, HMGB2, TPX2, ZBTB16, TRIP13
10942	2.11E-03	positive regulation of cell death	BID, STEAP3, JUN, ZBTB16, PMAIP1, MYC
9891	2.25E-03	positive regulation of biosynthetic process	EGR1, CDK1, FOS, HMGB2, HSP90AA1, JUN, TPX2, TOP2A, MYC
51246	2.38E-03	regulation of protein metabolic process	CCNB1, TNXB, SOCS3, JUN, SNCA, TPX2, UBE2C
31323	2.44E-03	regulation of cellular metabolic process	EGR1, CDK1, HMGB2, TNXB, HSP90AA1, SOCS3, SNCA, TPX2, ZBTB16, MCM5, CCNB1, FOS, UHRF1, JUN, GADD45G, ASF1B, MYC, TOP2A, HELLS
48477	2.50E-03	oogenesis	CCNB1, TPX2, TRIP13
32504	2.54E-03	multicellular organism reproduction	CCNB1, XDH, HMGB2, TPX2, ZBTB16, RACGAP1, TRIP13
48609	2.54E-03	reproductive process in a multicellular organism	CCNB1, XDH, HMGB2, TPX2, ZBTB16, RACGAP1, TRIP13
6461	2.54E-03	protein complex assembly	CCNB1, LCN2, CDK1, RRM2, TUBA4A, MYC
70271	2.54E-03	protein complex biogenesis	CCNB1, LCN2, CDK1, RRM2, TUBA4A, MYC
51054	2.57E-03	positive regulation of DNA metabolic process	CDK1, HMGB2, JUN
44267	2.66E-03	cellular protein metabolic process	CDK1, HSP90AA1, FKBP5, AURKA, PBK, UBE2C, CCNB1, HSPH1, PLK1, GADD45G, HSPD1, MELK, HSPA8, HSPA9
7131	2.81E-03	reciprocal meiotic recombination	TRIP13, RAD51
60045	2.81E-03	positive regulation of cardiac muscle cell proliferation	CCNB1, CDK1
19538	3.18E-03	protein metabolic process	CDK1, HSP90AA1, FKBP5, AURKA, PBK, UBE2C, CCNB1, HSPH1, CTSK, PLK1, GADD45G, HSPD1, MYC, MELK, HSPA8, HSPA9

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GO-ID	corrected p-value	Description	Genes in test set
9607	3.18E-03	response to biotic stimulus	LCN2, HSP90AA1, KRT8, FCER1G, HSPD1, HSPA1B
31497	3.39E-03	chromatin assembly	CENPA, ASF1B, HELLS
65008	3.39E-03	regulation of biological quality	XDH, BID, EGR1, APLNR, CTSK, CCNB2, JUN, SNCA, NUF2, LTF, HSPA1B, TACC3
16310	3.51E-03	phosphorylation	CCNB1, CDK1, PLK1, GADD45G, SNCA, AURKA, PBK, MELK, TK1
80090	3.61E-03	regulation of primary metabolic process	EGR1, CDK1, HMGB2, TNXB, SOCS3, SNCA, TPX2, ZBTB16, UBE2C, MCM5, CCNB1, FOS, UHRF1, JUN, ASF1B, MYC, TOP2A, HELLS
31399	3.76E-03	regulation of protein modification process	CCNB1, TNXB, SOCS3, JUN, SNCA
65004	3.92E-03	protein-DNA complex assembly	CENPA, ASF1B, HELLS
10628	3.92E-03	positive regulation of gene expression	LCN2, EGR1, CDK1, FOS, HMGB2, JUN, TOP2A, MYC
51254	3.92E-03	positive regulation of RNA metabolic process	CCNB1, EGR1, FOS, HMGB2, JUN, TOP2A, MYC
33209	3.94E-03	tumor necrosis factor-mediated signaling pathway	KRT18, KRT8
42326	4.04E-03	negative regulation of phosphorylation	CCNB1, JUN, SNCA
7276	4.04E-03	gamete generation	CCNB1, HMGB2, TPX2, ZBTB16, RACGAP1, TRIP13
9605	4.18E-03	response to external stimulus	FOS, S100A8, JUN, S100A9, FCER1G, MYC
31400	4.18E-03	negative regulation of protein modification process	CCNB1, JUN, SNCA
45935	4.47E-03	positive regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolic process	CCNB1, EGR1, CDK1, FOS, HMGB2, JUN, TOP2A, MYC
45936	4.57E-03	negative regulation of phosphate metabolic process	CCNB1, JUN, SNCA
10563	4.57E-03	negative regulation of phosphorus metabolic process	CCNB1, JUN, SNCA
32268	5.00E-03	regulation of cellular protein metabolic process	CCNB1, TNXB, SOCS3, JUN, SNCA, TPX2
60706	5.19E-03	cell differentiation involved in embryonic placenta development	SOCS3, KRT8
45214	5.19E-03	sarcomere organization	KRT8, TTN
43524	5.19E-03	negative regulation of neuron apoptosis	SNCA, BIRC5, RAD51
10557	5.37E-03	positive regulation of macromolecule biosynthetic process	EGR1, CDK1, FOS, HMGB2, JUN, TPX2, TOP2A, MYC
42325	5.73E-03	regulation of phosphorylation	CCNB1, TNXB, SOCS3, JUN, GADD45G, SNCA
55021	5.73E-03	regulation of cardiac muscle tissue growth	CCNB1, CDK1
55024	5.73E-03	regulation of cardiac muscle tissue development	CCNB1, CDK1
10165	5.73E-03	response to X-ray	PMAIP1, RAD51
60043	5.73E-03	regulation of cardiac muscle cell proliferation	CCNB1, CDK1
1556	5.73E-03	oocyte maturation	CCNB1, TRIP13
9889	5.85E-03	regulation of biosynthetic process	EGR1, CDK1, HMGB2, HSP90AA1, SNCA, S100A9, TPX2, ZBTB16, MCM5, FOS, UHRF1, JUN, ASF1B, MYC, TOP2A, HELLS
7292	5.96E-03	female gamete generation	CCNB1, TPX2, TRIP13

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GO-ID	corrected p-value	Description	Genes in test set
7143	6.48E-03	female meiosis	PLK1, TRIP13
31344	6.64E-03	regulation of cell projection organization	LCN2, HSP90AA1, LGALS1, CDC20
51174	6.74E-03	regulation of phosphorus metabolic process	CCNB1, TNXB, SOCS3, JUN, GADD45G, SNCA
19220	6.74E-03	regulation of phosphate metabolic process	CCNB1, TNXB, SOCS3, JUN, GADD45G, SNCA
6366	6.93E-03	transcription from RNA polymerase II promoter	FOS, JUN, MYC
19953	7.02E-03	sexual reproduction	CCNB1, HMGB2, TPX2, ZBTB16, RACGAP1, TRIP13
60420	7.08E-03	regulation of heart growth	CCNB1, CDK1
45453	7.08E-03	bone resorption	XDH, CTSK
7283	7.28E-03	spermatogenesis	HMGB2, TPX2, ZBTB16, RACGAP1, TRIP13
48232	7.28E-03	male gamete generation	HMGB2, TPX2, ZBTB16, RACGAP1, TRIP13
34622	7.66E-03	cellular macromolecular complex assembly	CENPA, TUBA4A, ASF1B, HELLS
6333	8.56E-03	chromatin assembly or disassembly	CENPA, ASF1B, HELLS
7051	8.73E-03	spindle organization	TPX2, TACC3
2706	8.75E-03	regulation of lymphocyte mediated immunity	CLEC2D, FCER1G, HSPA1B
51052	8.75E-03	regulation of DNA metabolic process	CDK1, HMGB2, JUN
3006	8.82E-03	reproductive developmental process	CCNB1, HMGB2, TPX2, ZBTB16, TRIP13
45944	8.82E-03	positive regulation of transcription from RNA polymerase II promoter	EGR1, FOS, HMGB2, JUN, TOP2A, MYC
7093	9.47E-03	mitotic cell cycle checkpoint	CDK1, MAD2L1
8104	9.51E-03	protein localization	BID, STEAP3, NUF2, ZBTB16, PMAIP1, TACC3, KIF20A, HSPA9