The critical information like platform, quality control, bioinformatics tools and the RNA sequencing data analysis (quality control, assembly, and mapping) *were exhibited in the following parts.*

Library preparation, and Illumina HiSeq xten Sequencing

RNA-seq transcriptome library construction and sequencing were performed using the TruSeq™ RNA sample preparation kit according to the manufacturer's instructions (Illumina, San Diego, CA, USA) at Shanghai Majorbio Bio-pharm Biotechnology Co., Ltd. (Shanghai, China). Firstly, poly(A) mRNA was purified according to the polyA selection method by oligo(dT) beads and then fragmented by fragmentation buffer. Secondly, the SuperScript double-stranded cDNA synthesis kit (Invitrogen, CA, USA) served to synthesize double-stranded cDNA with random hexamer primers (Illumina). Then the synthesized cDNA was subjected to end-repair, phosphorylation and 'A' base addition according to Illumina's library construction protocol. Libraries were size selected for cDNA target fragments of 200–300 bp on 2% Low Range Ultra Agarose followed by PCR amplified using Phusion DNA polymerase (New England Biolabs, Boston, MA) for 15 PCR cycles. After being quantified by TBS380 fluorometer (Turner Biosystems, USA), the paired-end RNA-seq sequencing library was sequenced utilizing the Illumina HiSeq xten sequencer (2 × 150bp read length).

Read mapping

The raw paired end reads were trimmed and quality controlled by SeqPrep (https://github.com/jstjohn/SeqPrep) and Sickle (https://github.com/najoshi/sickle) with default parameters. Then clean reads were separately aligned to reference genome with orientation mode using TopHat (http://tophat.cbcb.umd.edu/, version2.1.1) software. The mapping criteria was as follows: sequencing reads should be uniquely matched to the genome allowing up to 2 mismatches, without insertions or deletions. Then the region of genes was expanded following depths of sites and the operon was obtained. Furthermore, the whole genome was split into multiple 15k bp windows that share 5k bp. New transcribed regions were defined as more than 2 consecutive windows without overlapped region of gene, where at least 2 reads mapped per window in the same orientation.

Gene Expression Analysis

The data were analyzed on the free online platform of Majorbio Cloud Platform (www.majorbio.com). Briefly, to identify the differentially expressed genes (DEGs) between the different skin samples, the expression level of each transcript was calculated according to the fragments per kilobase of exon per million mapped reads (FRKM) method. RSEM (http://deweylab.biostat.wisc.edu/rsem/) was used to quantify gene abundances [1]. Statistical analysis of DEGs was conducted using the DESeq2 package.

A P value and the fold change (FC) for each gene were calculated to denote its expression difference between libraries. The DEGs between the control and inflamed skin samples were screened using $P < 0.01$ and $|\log_2 FC| > 3$ as the thresholds.

RNA Sequencing Data Analysis: Quality Control, Assembly, and Mapping

We analyzed the transcriptomes of the normal and *S. aureus*-infected skin samples via high-throughput RNA sequencing. Approximately 44.8 and 44.3 million raw reads were obtained from the control and model groups respectively. After removing low-quality reads, respectively 44.3 and 43.9 million high-quality reads from the control and model groups (>98.9% for both) were

assembled for downstream analysis. The clean reads were mapped to the reference genome (Genome assembly: GRCm38.p6, http://www.ensembl.org/Mus_musculus/Info/Index) and the detailed mapping output is summarized in the following Table A.

Table A. Summary of trimming and read mapping results of the sequences generated from the skin samples with or without the injection of *Staphylococcus aureus*.

Sample	Raw reads	Clean reads	Total reads	Total mapped	Multiple mapped	Uniquely mapped
Control1	45,022,032	44,445,246	44,445,246	42,720,677(96.12%)	3,242,878(7.3%)	39,477,799(88.82%)
Control2	44,633,900	44,348,374	44,348,374	42,988,527(96.93%)	3,280,302(7.4%)	39,708,225(89.54%)
Control3	44,768,108	44,227,922	44,227,922	42,503,298(96.1%)	3,238,662(7.32%)	39,264,636(88.78%)
Model1	43,619,658	43,337,052	43,337,052	41,713,031(96.25%)	2,676,494(6.18%)	39,036,537(90.08%)
Model2	44,876,888	44,364,064	44,364,064	42,687,638(96.22%)	2,632,583(5.93%)	40,055,055(90.29%)
Model3	44,517,200	44,270,602	44,270,602	42,717,763(96.49%)	2,922,110(6.6%)	39,795,653(89.89%)

Note: Control represents the skin sample of mice without the injection of *Staphylococcus aureus*; Model represents the skin sample of mice with the injection of *Staphylococcus aureus*. Three replicates of Control (Control-1, -2 and -3) and Model (Model-1, -2 and -3) treatments were carried out in RNA-seq analysis.

Reference
1. Li B, Dewey CN. RSEM: accurate transcript quantification from RNA-Seq data with or without a reference genome. BMC Bioinformatics 2011; 12:323. DOI: 10.1186/1471-2105-12-323.
2. Wang L, Feng Z, Wang X, et al. DEGseq: an R package for identifying differentially express ed genes from RNA-seq data. Bioinformatics, 2009, 26(1): 136-138. DOI:10.1093/bioinformatics/btp612

Fig. S1

Heatmap
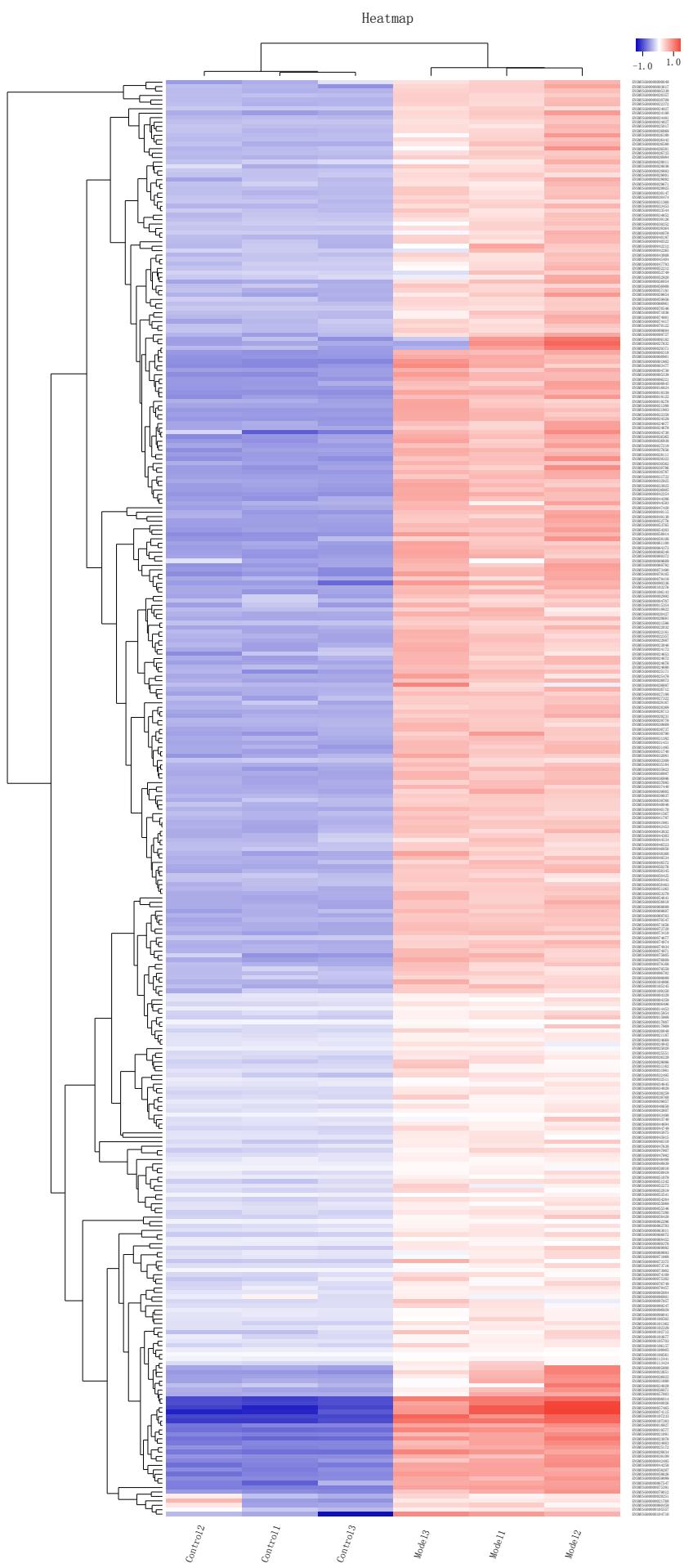
Fig. S2
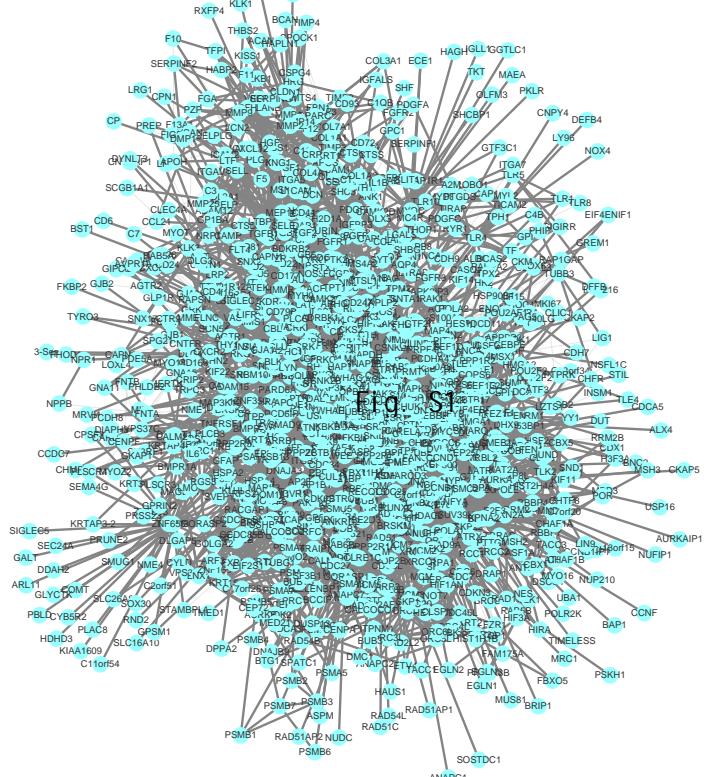
Fig. S3
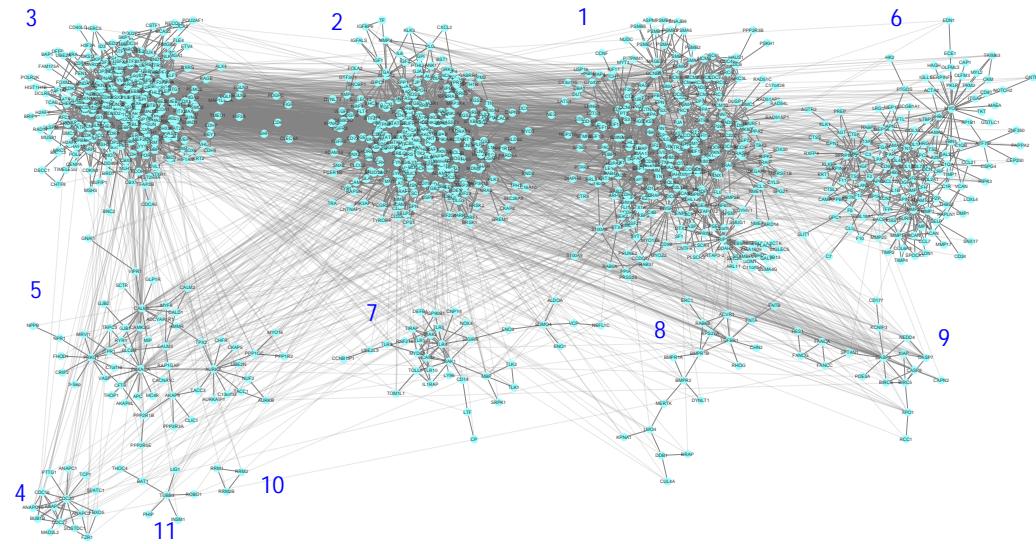
Table S1 Primer pairs of genes validated by qRT-PCR

Gene symbol	Sequence (5' - 3')	Length	Tm
Nox4	F: GAAGGGGTTAAACACCTCTGC	21	60.6
	R: ATGCTCTGCTTAAACACAATCCT	23	60.2
Mmrn1	F: GGTCTTCAGGCTTACCAACAC	21	60.6
	R: GAGTGGCCGAGAGCACTTG	19	62.7
Mcm5	F: CAGAGGCGATTCAAGGAGTTC	21	60.4
	R: CGATCCAGTATTCACCCAGGT	21	61.0
Msx1	F: TGCTGCTATGACTTCTTTGCC	21	60.6
	R: GCTTCCTGTGATCGGCCAT	19	62.1
Fgf5	F: AAGTAGCGCGACGTTTTCTTC	21	61.2
	R: CTGGAAACTGCTATGTTCCGAG	22	60.7

Table S2 GO clustering results of up-regulated DEGs

Categories	Term	Count	P-Value
Annotation Cluster 1 Acute-Phase Response			
Enrichment Score: 3.06			
BP	GO:0006953: acute-phase response	7	5.62E-06
CC	GO:0034364: high-density lipoprotein particle	4	2.69E-03
MF	GO:0042056: chemoattractant activity	3	4.39E-02
Annotation Cluster 2 Chemotaxis			
Enrichment Score: 2.86			
BP	GO:0060326: cell chemotaxis	9	8.24E-06
BP	GO:0006935: chemotaxis	10	2.54E-05
MF	GO:0005125: cytokine activity	8	2.56E-02
MF	GO:0008009: chemokine activity	4	2.65E-02
BP	GO:0070098: chemokine-mediated signaling pathway	4	3.54E-02
Annotation Cluster 3 Negative Regulation of Inflammation Factor Production			
Enrichment Score: 2.12			
BP	GO:0032689: negative regulation of interferon-gamma production	5	3.98E-04
BP	GO:0032720: negative regulation of tumor necrosis factor production	4	0.019
BP	GO:0032715: negative regulation of interleukin-6 production	3	0.059
Annotation Cluster 4 Lipid Metabolism			
Enrichment Score: 2.00			
CC	GO:0042627: chylomicron	4	6.26E-04
MF	GO:0060230: lipoprotein lipase activator activity	3	0.001
BP	GO:0010916: negative regulation of very-low-density lipoprotein particle clearance	3	0.002
CC	GO:0034363: intermediate-density lipoprotein particle	3	0.002
CC	GO:0034361: very-low-density lipoprotein particle	4	0.002
BP	GO:0048261: negative regulation of receptor-mediated endocytosis	3	0.002
MF	GO:0055102: lipase inhibitor activity	3	0.003
BP	GO:0034382: chylomicron remnant clearance	3	0.003
CC	GO:0034366: spherical high-density lipoprotein particle	3	0.005
BP	GO:0070328: triglyceride homeostasis	4	0.005
BP	GO:0010898: positive regulation of triglyceride catabolic process	3	0.007
BP	GO:0051006: positive regulation of lipoprotein lipase activity	3	0.009
BP	GO:0006869: lipid transport	6	0.015
BP	GO:0033700: phospholipid efflux	3	0.018
BP	GO:0001523: retinoid metabolic process	3	0.025

Note: Count represents the gene number.

Abbreviations: DEGs, differential expressed genes; BP, biological process; CC, cell comcomponent; MF, molecular function.

Table S3 GO clustering results of down-regulated DEGs

Categories	Term	Count	*P*-Value
Annotation Cluster 1 Cell Cycle			
Enrichment Score: 39.15			
BP	GO:0007049: cell cycle	65	2.58E-42
BP	GO:0051301: cell division	52	2.87E-39
BP	GO:0007067: mitotic nuclear division	46	4.73E-38
Annotation Cluster 2 Chromosome Segregation			
Enrichment Score: 20.58			
BP	GO:0007067: mitotic nuclear division	46	4.73E-38
CC	GO:0000775: chromosome, centromeric region	25	1.69E-20
CC	GO:0005694: chromosome	34	8.92E-20
BP	GO:0007059: chromosome segregation	20	7.50E-19
CC	GO:0000776: kinetochore	22	2.45E-18
CC	GO:0000777: condensed chromosome kinetochore	15	2.59E-12
Annotation Cluster 3 Structural Molecule			
Enrichment Score: 9.10			
CC	GO:0005882: intermediate filament	16	2.14E-11
CC	GO:0045095: keratin filament	14	4.56E-10
MF	GO:0005198: structural molecule activity	17	5.07E-08
Annotation Cluster 4 Microtubule-Based Movement			
Enrichment Score: 8.72			
CC	GO:0005874: microtubule	24	3.04E-11
CC	GO:0005871: kinesin complex	12	3.94E-11
BP	GO:0007018: microtubule-based movement	13	1.43E-10
MF	GO:0003777: microtubule motor activity	13	1.73E-10
MF	GO:0008017: microtubule binding	18	6.19E-10
BP	GO:0007080: mitotic metaphase plate congression	9	5.25E-09
MF	GO:0016887: ATPase activity	10	9.77E-04
Annotation Cluster 5 Melanin Biosynthetic Process			
Enrichment Score: 4.42			
BP	GO:0042438: melanin biosynthetic process	6	2.83E-07
CC	GO:0033162: melanosome membrane	5	1.13E-05
BP	GO:0043473: pigmentation	4	0.02
Annotation Cluster 6 DNA Metabolism			
Enrichment Score: 2.21			
CC	GO:0000793: condensed chromosome	5	5.23E-04
BP	GO:0006259: DNA metabolic process	4	0.002
MF	GO:0008022: protein C-terminus binding	5	0.27

Note: Count represents the gene number.

Abbreviations: DEGs, differential expressed genes; BP, biological process; CC, cell comcomponent; MF, molecular function

Table S4 Detailed information of the hubs.

name	Average Shortest PathLength	Betweenness Centrality	Closeness Centrality	Neighborhood Connectivity	Number Of Directed Edges	Degree
CDK1	2.67030717	0.06518027	0.37448875	15.36134454	119	119
TP53	2.52354949	0.06261685	0.39626724	25.15740741	108	108
BRCA1	2.65255973	0.04757682	0.37699434	22.50943396	106	106
ESR1	2.66825939	0.0276148	0.37477616	28.51898734	79	79
CSNK2A1	2.64368601	0.04554386	0.37825975	22.11267606	71	71
CREBBP	2.72696246	0.01900886	0.36670839	27.37681159	69	69
AR	2.65324232	0.01944033	0.37689735	31.47826087	69	69
SMAD3	2.74266212	0.02305794	0.36460926	26.26470588	68	68
EP300	2.76723549	0.013427	0.36137148	29.21212121	66	66
EGFR	2.73242321	0.02619649	0.36597552	25.83076923	65	65
GRB2	2.84095563	0.0216046	0.35199423	21.71428571	63	63
RB1	2.76518771	0.01842844	0.3616391	25.98412698	63	63
PRKCA	2.74607509	0.0353015	0.3641561	19.86666667	60	60
MAPK1	2.75017065	0.01592446	0.3636138	27.62711864	59	59
SHC1	2.86348123	0.01143227	0.34922527	26.98113208	53	53
YWHAG	2.79590444	0.02318452	0.35766602	20.54716981	53	53
FYN	2.78566553	0.01822229	0.35898064	25.75471698	53	53
CDK2	2.98225256	0.01346032	0.33531701	20.83018868	53	53
STAT3	2.81638225	0.01403299	0.35506544	29.80769231	52	52
PIK3R1	2.82116041	0.0143178	0.35446407	27.46	50	50
ABL1	2.6996587	0.02424667	0.37041719	31.53061224	49	49
SMAD2	2.8116041	0.01425885	0.35566885	28.67346939	49	49
CASP3	2.81911263	0.01322838	0.35472155	23.48979592	49	49
HDAC1	2.85802048	0.0112794	0.34989252	28.32653061	49	49
CTNNB1	2.77201365	0.01830074	0.36074858	29.32653061	49	49
RELA	2.81023891	0.00879414	0.35584163	31.02083333	48	48
PLK1	3.02662116	0.02026808	0.33040144	13.27659574	47	47
SMAD4	2.79385666	0.01458847	0.35792817	29.02222222	45	45
SP1	2.84163823	0.0069641	0.35190968	34.66666667	45	45
PRKACA	2.97474403	0.01611233	0.33616338	17.04545455	44	44
LCK	2.85802048	0.00750143	0.34989252	28.90909091	44	44
NR3C1	2.84914676	0.00856867	0.35098227	30.18181818	44	44
STAT1	2.87167235	0.01158159	0.34822914	28.13636364	44	44

JUN	2.85187713	0.00606078	0.35064624	33.25	44	44
TRIP13	3.39249147	0.02728862	0.29476861	4.86046512	43	43
PTPN11	2.98020478	0.00598381	0.33554741	28.19047619	42	42
MAPK3	2.87235495	0.0064558	0.34814639	26.0952381	42	42
AKT1	2.82798635	0.00810623	0.3536085	29.76190476	42	42
PRKCD	2.84163823	0.01008381	0.35190968	28.95121951	41	41
CBL	2.96518771	0.00783802	0.33724678	29.95121951	41	41
VIM	2.87849829	0.01468694	0.34740337	20.6	40	40
LYN	2.88600683	0.01024751	0.34649953	26.23076923	39	39
PTPN6	2.94334471	0.00842894	0.33974954	28.33333333	39	39
MYC	2.88327645	0.00633811	0.34682765	32.23076923	39	39
SYK	2.98225256	0.01019946	0.33531701	26.25641026	39	39
MYOC	3.19317406	0.02182762	0.31316802	7.47368421	38	38
RAF1	2.89010239	0.00776477	0.3460085	30.36842105	38	38
CDKN1A	2.92354949	0.00742643	0.34204996	27.54054054	37	37
YWHAZ	2.89078498	0.00798263	0.3459268	25.47222222	36	36
PCNA	3.07372014	0.00821515	0.32533866	20.80555556	36	36
TGFBR1	2.92354949	0.01531915	0.34204996	21.22222222	36	36
MDM2	2.90375427	0.00882197	0.34438176	32.13888889	36	36
UBE2I	2.92696246	0.01486245	0.34165112	26.51428571	35	35
PIN1	2.84163823	0.01186664	0.35190968	28.28571429	35	35
PLCG1	3.04982935	0.00659668	0.3278872	25.6	35	35
MMP2	3.378157	0.01535252	0.2960194	8.38235294	34	34
TRAF2	3.1003413	0.01407148	0.32254513	14.02941176	34	34
FN1	3.17952218	0.01858716	0.31451267	12.88235294	34	34
PTK2	2.94744027	0.0054353	0.33927744	30.18181818	33	33
CAV1	2.87372014	0.01425034	0.347981	30.42424242	33	33
JAK2	2.95290102	0.0037805	0.33865002	33.45454545	33	33
CSNK2A2	2.98225256	0.0063947	0.33531701	19.125	32	32
VAV1	3.00409556	0.00491544	0.33287889	28.59375	32	32
NFKB1	2.98430034	0.00304166	0.33508692	29.3125	32	32
CALM1	2.97952218	0.01747462	0.33562428	21.4375	32	32
IRS1	2.96518771	0.00384899	0.33724678	32.32258065	31	31
STAT5A	2.96791809	0.00208742	0.33693652	36.48387097	31	31
GSK3B	2.99658703	0.00388009	0.33371298	24.87096774	31	31
KAT5	2.90170648	0.00598959	0.34462479	34.36666667	30	30
YWHAB	2.99249147	0.00333619	0.33416971	24.23333333	30	30
PML	2.9331058	0.00338986	0.34093554	35.36666667	30	30
HSP90AA1	2.821843	0.01119515	0.35437833	37.73333333	30	30
RXRA	3.00887372	0.00524478	0.33235027	25.1	30	30

TBP	3.0559727	0.00299006	0.32722805	28.03333333	30	30
ZBTB16	2.94129693	0.01127089	0.33998608	28.43333333	30	30
XRCC6	2.9665529	0.00951465	0.33709158	26.31034483	29	29
YWHAE	2.96109215	0.00436169	0.33771323	25	29	29
UBB	2.89829352	0.00575859	0.34503062	32.10344828	29	29
CASP8	2.96996587	0.00442019	0.33670421	27.44827586	29	29
PDGFR B	3.09897611	0.00253878	0.32268722	29.72413793	29	29
NFKBIA	2.98225256	0.00577504	0.33531701	25.51724138	29	29
CCNB1	3.04505119	0.00688436	0.3284017	22.79310345	29	29
MCM10	3.4552901	0.00386625	0.2894113	13.78571429	28	28
EWSR1	2.9774744	0.01836635	0.33585511	18	28	28
SUMO1	3.06006826	0.0051607	0.3267901	25.14285714	28	28
UBQLN 4	3.07235495	0.01300429	0.32548323	13.89285714	28	28
MCM7	3.27576792	0.00316274	0.30527193	18.28571429	28	28
RAD51	3.07576792	0.01099833	0.32512206	23.07142857	28	28
IGFBP3	3.0996587	0.01347889	0.32261616	14.75	28	28
CRK	3.04846416	0.00280804	0.32803403	30.44444444	27	27
ATM	3.13651877	0.00237084	0.31882481	23.51851852	27	27
PIAS1	2.98156997	0.00184852	0.33539377	34.03703704	27	27
HDAC2	3.01023891	0.00370765	0.33219955	28.33333333	27	27
CCNA2	3.08805461	0.00416521	0.32382847	27.77777778	27	27
CCND1	2.96109215	0.00529778	0.33771323	34.85185185	27	27
IGF1R	2.98225256	0.00781287	0.33531701	29.25925926	27	27
KNG1	3.41501706	0.01077378	0.29282431	9.22222222	27	27
MAPK1 4	2.99453925	0.00248359	0.33394119	27.40740741	27	27
SMAD1	3.0662116	0.00696736	0.32613535	22.14814815	27	27
CDKN1 B	3.03208191	0.00441235	0.32980639	27.26923077	26	26
KDR	3.09419795	0.00816904	0.32318553	24.73076923	26	26
ATXN1	3.02525597	0.0083183	0.33055054	18.30769231	26	26
FLNA	2.9112628	0.01142461	0.34349355	22	26	26
E2F1	3.06211604	0.00160328	0.32657156	33.19230769	26	26
PRKG1	3.27849829	0.00600271	0.3050177	9.76	25	25
CDK4	3.09488055	0.00367651	0.32311425	25.88	25	25
ACTB	3.04505119	0.00737685	0.3284017	18.16	25	25
BCR	3.03481229	0.00212821	0.32950967	33.28	25	25
CHEK1	3.05802048	0.00406268	0.32700893	25.56	25	25
BTK	2.97542662	0.00865862	0.33608626	28.84	25	25
PPP1CA	3.03208191	0.00717457	0.32980639	26.88	25	25
PDGFR	3.24982935	0.00406691	0.30770846	21.48	25	25

A					
PPP2CA	3.01979522	0.01089583	0.33114828	27.91666667	24	24
RASA1	3.09419795	0.00424925	0.32318553	29.875	24	24
BARD1	3.12354949	0.00382426	0.3201486	22.5	24	24
HIF1A	3.00409556	0.00717564	0.33287889	34.58333333	24	24
STAT5B	3.08600683	9.51E-04	0.32404335	33.41666667	24	24
SVIL	3.04573379	0.01170591	0.3283281	16.29166667	24	24
PIAS4	3.05460751	0.00260673	0.3273743	29.75	24	24
YWHAH	3.08054608	0.00696476	0.32461777	25.54166667	24	24
ATN1	3.15699659	0.00918998	0.31675676	12.83333333	24	24
NCOR2	3.09624573	0.00122534	0.32297178	30.54166667	24	24
BCL2	2.97610922	0.00292659	0.33600917	32.73913043	23	23
AURKA	3.14880546	0.00971948	0.31758075	19.7826087	23	23
CHUK	2.97474403	0.00202717	0.33616338	35.82608696	23	23
CDC25C	3.00409556	0.00384551	0.33287889	29.86956522	23	23
APP	3.03412969	0.00945352	0.3295838	22.34782609	23	23
EEF1A1	3.01365188	0.00833138	0.33182333	21.52173913	23	23
MCM2	3.45119454	0.00120939	0.28975475	17.65217391	23	23
PTPN1	2.94607509	0.00184931	0.33943466	41.39130435	23	23
POU2F1	3.13720137	0.00244616	0.31875544	29.86956522	23	23
JAK1	3.03617747	0.00248688	0.32936151	33.82608696	23	23
NCOA1	3.11740614	8.26E-04	0.32077951	34.13043478	23	23
HMGB1	2.96177474	0.01055407	0.3376354	29.36363636	22	22
PLG	3.46279863	0.01074367	0.28878376	10.63636364	22	22
TLR4	3.46552901	0.00956087	0.28855623	9.04545455	22	22
CHD3	3.14539249	0.00209535	0.31792535	22.27272727	22	22
HGS	3.07030717	0.00566265	0.32570031	21.63636364	22	22
SMAD9	3.15767918	0.00674919	0.31668828	16.54545455	22	22
SRF	3.14948805	0.00193088	0.31751192	23.68181818	22	22
PRKCB	3.04368601	0.00612833	0.328549	20.31818182	22	22
SKIL	3.14812287	0.00589073	0.31764961	21.68181818	22	22
CHEK2	3.19590444	0.0060305	0.31290047	24.71428571	21	21
CDC20	3.40204778	0.00586971	0.29394061	12.95238095	21	21
CDC6	3.44368601	0.00305429	0.29038652	19.28571429	21	21
SKP2	3.32559727	0.00145107	0.30069787	19.95238095	21	21
LEF1	3.22116041	0.00460632	0.31044713	21.23809524	21	21
TNFRSF1A	3.06484642	0.0046247	0.32628062	30.38095238	21	21
EZR	3.08532423	0.00582644	0.32411504	22.38095238	21	21
MAPT	2.9665529	0.002593	0.33709158	32.04761905	21	21
PARP1	3.1440273	0.00503342	0.3180634	23.71428571	21	21
CD5	3.16450512	0.0039935	0.31600518	24.23809524	21	21

RBL1	3.20546075	0.00114501	0.31196763	28.42857143	21	21
THBS1	3.58156997	0.00429665	0.27920717	14.61904762	21	21
CSNK2B	2.9447099	0.00448107	0.33959203	40	21	21
PLSCR1	3.14061433	0.00645011	0.31840904	19.38095238	21	21
YWHAQ	3.04982935	0.00473007	0.3278872	21.28571429	21	21
ZAP70	3.23549488	0.00176937	0.30907173	28	21	21
KRT18	2.96450512	0.00350686	0.33732443	36.57142857	21	21
C1orf103	3.30784983	0.00296971	0.30231118	13.71428571	21	21
MCM3	3.38771331	0.00226063	0.29518436	19.47619048	21	21
KHDRBS1	2.98156997	0.00773879	0.33539377	39.47619048	21	21
RACGAP1	3.29897611	0.00723803	0.30312435	12.2	20	20
TUBA4A	3.01501706	0.00726483	0.33167308	28.75	20	20
TOP2A	2.94607509	0.00343118	0.33943466	41.4	20	20
MDM4	3.00887372	0.00109124	0.33235027	43.85	20	20
CD44	3.15767918	0.00764187	0.31668828	19.55	20	20
ORC2L	3.59317406	4.70E-04	0.27830547	17.55	20	20
HRAS	3.15017065	0.00347734	0.31744312	22.75	20	20