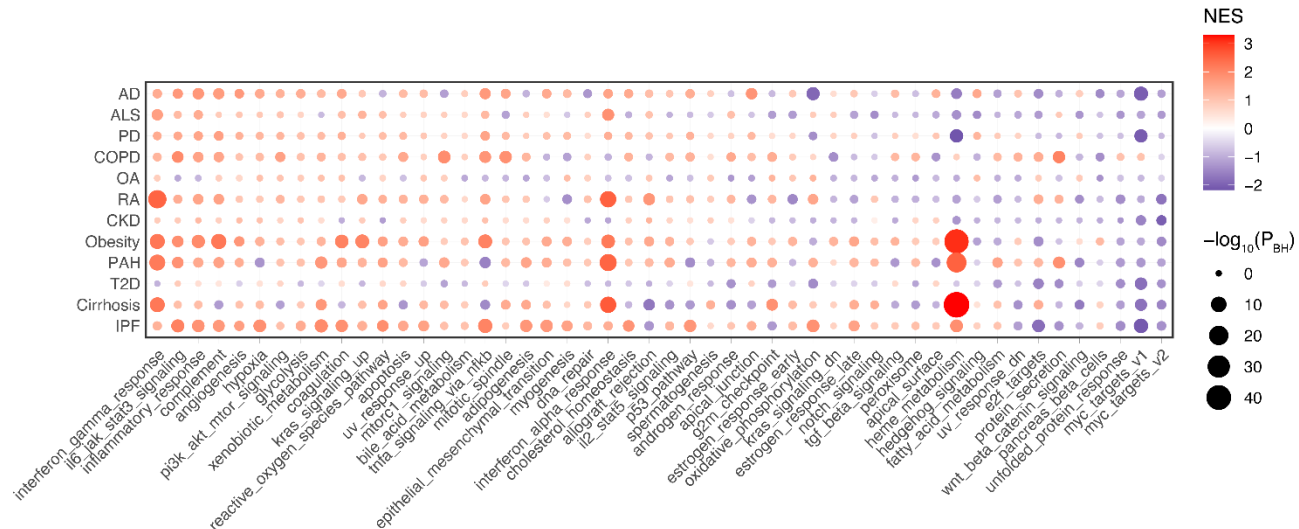


SUPPLEMENTARY DATA

Integrating AI and Causal Genetics to Prioritize Therapeutic Targets for Aging and Age-Related Diseases

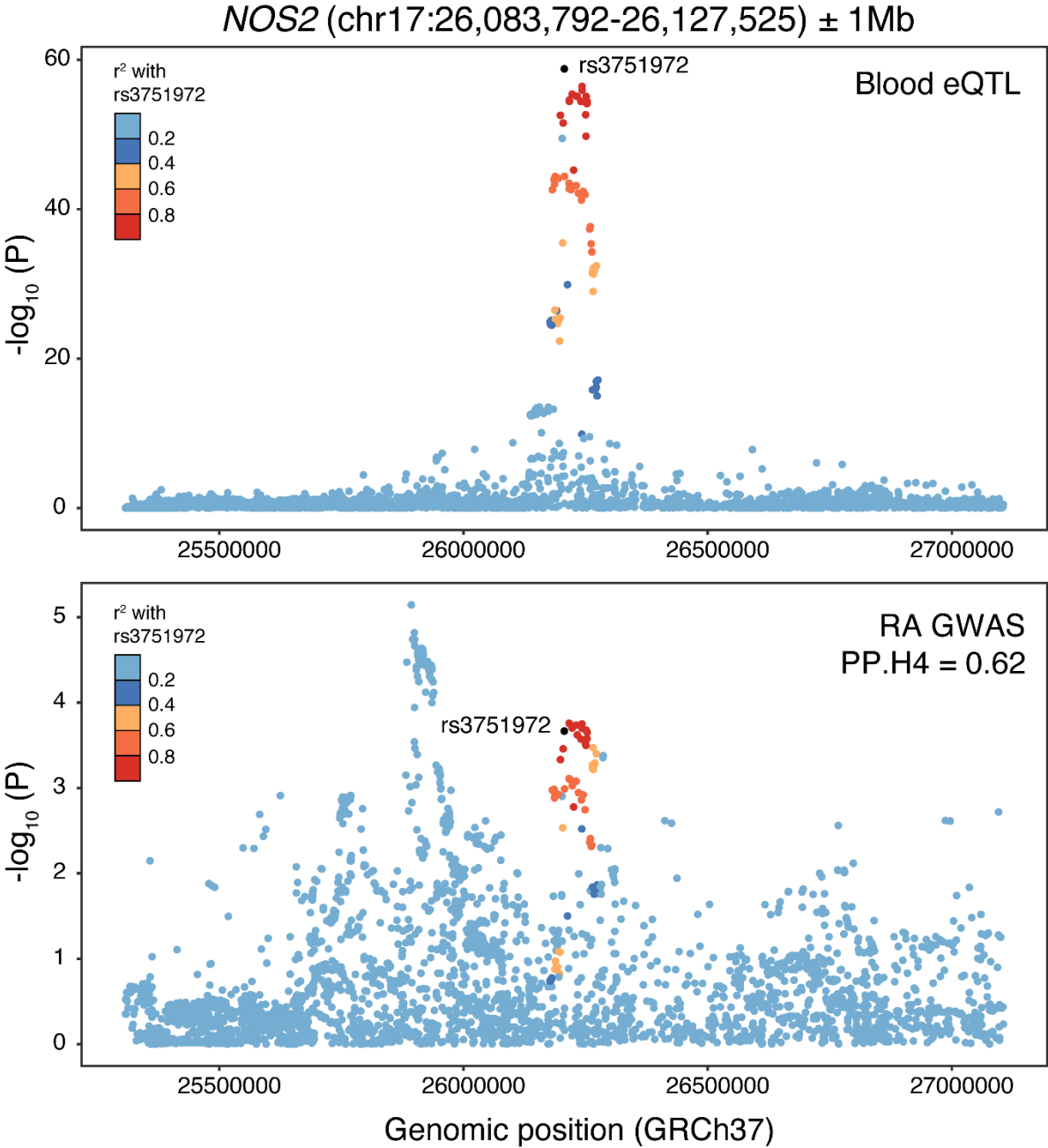
Geoffrey H. D. Leung, Jianjiu Chen, I. Aylin Ergun, Evgeny Izumchenko, Alex Aliper, Feng Ren, Frank W. Pun, Alex Zhavoronkov

SUPPLEMENTARY DATA



Supplementary Figure 1. Perturbation of the 50 analyzed hallmark gene sets in 12 ARDs. Red, NES > 0; Blue, NES < 0. NES = Normalized enrichment score. P_{BH} = Benjamini-Hochberg-corrected P value.

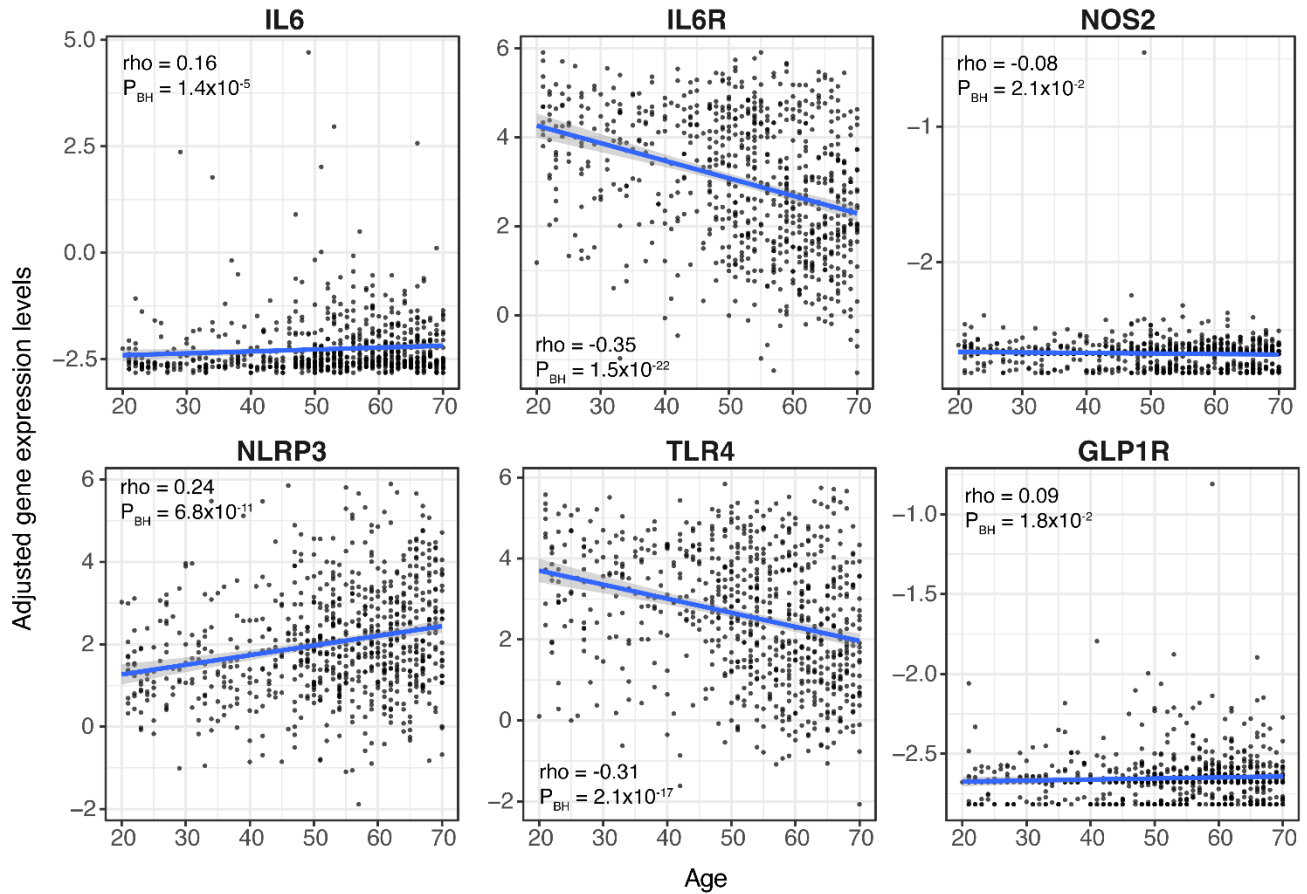
SUPPLEMENTARY DATA



Supplementary Figure 3. Colocalization analysis showing moderately shared genetic signals between *NOS2* expression and rheumatoid arthritis risk at the *NOS2* locus. Each dot represents 1 genetic variant. Colors represent LD with the lead variant (rs3751972) in the blood eQTL.

SUPPLEMENTARY DATA

Gene expression levels of shortlisted target genes in whole blood (n=755)



Supplementary Figure 4. Correlation between the gene expression levels of 6 shortlisted target genes and age in whole blood measured in the GTEx cohort (n=755). Gene expression levels were adjusted for sex. Blue line = best fit line obtained from linear regression. Rho = Spearman's correlation coefficient. P_{BH} = Benjamini-Hochberg-corrected P value.

SUPPLEMENTARY DATA

Supplementary Table 1. Datasets analyzed in the current study for target prioritization.

Disease area	Disease	Dataset	No. of cases	No. of controls	Data type
Aging	Aging	GSE58137	19	172	Microarray
Aging	Aging	GSE123698	42	26	Microarray
Aging	Aging	GSE75337	14	16	RNA-seq
Aging	Aging	GSE16717	50	50	Microarray
Neurological	Alzheimer's disease	GSE63060	145	104	Microarray
Neurological	Alzheimer's disease	GSE140829	204	249	Microarray
Neurological	Alzheimer's disease	GSE18309	3	3	Microarray
Neurological	Alzheimer's disease	GSE134576	3	4	RNA-seq
Neurological	Alzheimer's disease	GSE136243	74	41	RNA-seq
Neurological	Alzheimer's disease	GSE161199	6	10	RNA-seq
Neurological	Alzheimer's disease	GSE97760	9	10	Microarray
Neurological	Alzheimer's disease	GSE63061	139	134	Microarray
Neurological	Alzheimer's disease	E-MTAB-6094	22	13	Microarray
Neurological	ALS	GSE112680	164	137	Microarray
Neurological	ALS	GSE234297	96	48	RNA-seq
Neurological	ALS	GSE183204	18	12	RNA-seq
Metabolic	CKD	GSE97709	8	12	RNA-seq
Metabolic	CKD	GSE43484	3	3	Microarray
Metabolic	CKD	GSE15072	9	8	Microarray
Inflammatory	COPD	GSE71220	405	57	Microarray
Inflammatory	COPD	GSE124180	6	15	RNA-seq
Inflammatory	COPD	GSE118468	15	6	Methylation
Fibrotic	Cirrhosis of liver	E-MTAB-3338	30	8	Microarray
Fibrotic	Cirrhosis of liver	GSE142255	14	7	Microarray
Fibrotic	Cirrhosis of liver	GSE123932	6	6	Microarray
Fibrotic	IPF	GSE93606	154	20	Microarray
Fibrotic	IPF	GSE33566	93	30	Microarray
Fibrotic	IPF	GSE38958	60	35	Microarray
Metabolic	Obesity	E-MTAB-54	45	23	Microarray
Metabolic	Obesity	GSE110551	39	39	Microarray
Metabolic	Obesity	GSE109597	16	43	Microarray
Inflammatory	Osteoarthritis	GSE48556	106	33	Microarray
Neurological	Parkinson's disease	GSE99039	191	200	Microarray
Neurological	Parkinson's disease	GSE6613	50	22	Microarray
Neurological	Parkinson's disease	GSE155700	17	12	RNA-seq
Neurological	Parkinson's disease	GSE72267	40	19	Microarray
Neurological	Parkinson's disease	GSE34287	19	12	Microarray
Metabolic	Pulmonary arterial hypertension	GSE703	7	6	Microarray

SUPPLEMENTARY DATA

Metabolic	Pulmonary arterial hypertension	GSE131793	5	10	Microarray
Metabolic	Pulmonary arterial hypertension	GSE33463	30	41	Microarray
Metabolic	Pulmonary arterial hypertension	GSE38267	13	28	Microarray
Inflammatory	Rheumatoid arthritis	GSE120178	125	20	RNA-seq
Inflammatory	Rheumatoid arthritis	GSE93272	232	43	Microarray
Inflammatory	Rheumatoid arthritis	GSE111942	25	18	Methylation
Inflammatory	Rheumatoid arthritis	GSE90081	5	12	RNA-seq
Metabolic	T2DM	GSE184050	25	33	RNA-seq
Metabolic	T2DM	GSE280402	8	8	RNA-seq
Metabolic	T2DM	GSE154881	5	5	RNA-seq
Metabolic	T2DM	GSE21321	9	8	Microarray
Metabolic	T2DM	GSE23561	8	7	Microarray
Metabolic	T2DM	GSE15932	8	8	Microarray

SUPPLEMENTARY DATA

Supplementary Table 2. GWAS summary statistics datasets analyzed in the current study.

Accession ID/URL	Trait	Discovery sample description	First author	PubMed ID	Year
GCST002245	Alzheimer's disease	17,008 European ancestry cases, 37,154 European ancestry controls	Lambert JC	24162737	2013
GCST009324	Parkinson's disease	15,056 European ancestry cases, 12,637 European ancestry controls	Nalls MA	31701892	2019
GCST004692	Amyotrophic lateral sclerosis	12,577 European ancestry cases, 23,475 European ancestry controls	van Rheenen W	27455348	2016
GCST90399694	Chronic obstructive pulmonary disease	58,559 European ancestry cases, 937,358 European ancestry controls	Zhou W	36777996	2022
GCST90476383	Osteoarthritis	49,976 European ancestry cases, 265,692 European ancestry controls	Verma A	39024449	2024
GCST90132226	Rheumatoid arthritis	17,221 European ancestry cases, 74,823 European ancestry controls	Ishigaki K	36333501	2022
GCST008065	Chronic kidney disease	up to 64,164 European ancestry cases, up to 561,055 European ancestry controls	Wuttke M	31152163	2019
GCST90475762	Obesity	169,600 European ancestry cases, 244,254 European ancestry controls	Verma A	39024449	2024
GCST007228	Pulmonary arterial hypertension	2,085 European ancestry cases, 9,659 European ancestry controls	Rhodes CJ	30527956	2018
GCST005047	Type 2 diabetes mellitus	6,377 European ancestry male cases, 5,794 European ancestry female cases, 22,243 European ancestry male controls, 34,619 European ancestry female controls	Morris AP	22885922	2012
GCST90319877	Cirrhosis of liver	15,225 European ancestry cases, 1,564,786 European ancestry controls	Ghouse J	38632349	2024
GCST90399720	Idiopathic pulmonary fibrosis	6,257 European ancestry cases, 947,616 European ancestry controls	Zhou W	36777996	2022
GCST008598	Longevity	11,262 European ancestry cases, 25,483 European ancestry controls	Deelen J	31413261	2019
GCST90020053	Frailty index	175,226 European ancestry individuals	Atkins JL	34431594	2021
http://dx.doi.org/10.7488/ds/2463	Parental survival	1,012,240 parents of European ancestry	Timmers PR	30642433	2019

SUPPLEMENTARY DATA

Supplementary Table 3. Top 100-ranked aging-related high-confidence targets

Gene	Rank
CDKN2A	1
PTPN11	2
JAK2	3
SOD1	4
VEGFA	5
PPARA	6
NFKB2	7
HIF1A	8
MAPK8	9
BLM	10
IL6	11
NFKB1	12
EGFR	13
FOXO1	14
FOS	15
TNF	16
PPARG	17
AKT1	18
SIRT1	19
MAPK3	20
STAT3	21
CDKN1A	22
EGF	23
TGFB1	24
FOXO3	25
WRN	26
TP53	27
MYC	28
BDNF	29
MTOR	30
PPARGC1A	31
CDK1	32
CREB1	33
GSK3B	34
TERT	35
APP	36
AR	37
CLOCK	38
NFKBIA	39
ERCC1	40
RELA	41
KL	42
JUN	43
IL2	44
ESR1	45
IGF1	46
HDAC1	47
IRS1	48
LMNA	49
MDM2	50
CCNA2	51
APOE	52

SUPPLEMENTARY DATA

IKBKB	53
SIRT6	54
AGTR1	55
CAT	56
GDF11	57
SHC1	58
HDAC3	59
NFE2L2	60
PSEN1	61
MAPK9	62
SP1	63
PIK3R1	64
PCNA	65
TP53BP1	66
E2F1	67
CNR1	68
MAPK14	69
CTNNB1	70
CDC42	71
PDGFRB	72
PIN1	73
CEBPA	74
PIK3CA	75
IL7R	76
CDKN2B	77
LMNB1	78
ABL1	79
HMGB1	80
ATM	81
HDAC2	82
BAX	83
EGR1	84
PTK2	85
CEBPB	86
NCOR2	87
ELN	88
S100B	89
SIN3A	90
MAPT	91
HSF1	92
PTGS2	93
FOXO1	94
XPA	95
SIRT3	96
MIF	97
SERPINE1	98
GRB2	99
BUB1B	100

SUPPLEMENTARY DATA

Supplementary Table 4. Top 100-ranked aging-related novel targets

Gene	Rank
CXCL8	1
CD19	2
IL3	3
CASP3	4
TLR4	5
SNCA	6
TH	7
HDAC4	8
AKT2	9
NLRP3	10
DNMT1	11
FYN	12
IL1B	13
ADORA2A	14
NOS2	15
NTRK1	16
NOS3	17
CYCS	18
CD28	19
CCND1	20
WNK2	21
SMAD3	22
CD44	23
TGFBR1	24
CCL2	25
DNMT3A	26
VIM	27
SOX2	28
IL4	29
CAV1	30
RTEL1	31
RXRA	32
CXCR4	33
ARNT	34
MAPK1	35
GRIN2B	36
GLB1	37
PECAM1	38
OGG1	39
CDK4	40
NR3C2	41
SOCS3	42
RUNX2	43
C3	44
HTRA1	45
AGT	46
RHO	47
GFAP	48
CTBP1	49
ALB	50
STING1	51
PLK1	52
SMAD4	53

SUPPLEMENTARY DATA

ICAM1	54
LAMB2	55
CXCL6	56
MMP9	57
AKT3	58
PTPRC	59
ARMS2	60
IL18	61
MMP7	62
PARP2	63
BRAF	64
MET	65
ADRB1	66
MYB	67
COL1A1	68
GJA1	69
REST	70
PIK3CD	71
HSPA5	72
EPAS1	73
ESR2	74
H3-4	75
NR5A1	76
XPO1	77
IKBKG	78
DCX	79
APOB	80
FOSB	81
GCG	82
SELENOP	83
CASP8	84
ADRA1D	85
ITGAM	86
VDR	87
AHR	88
KIT	89
H2BC21	90
SRC	91
MMP13	92
JAK1	93
IDH1	94
SPP1	95
ATF4	96
THBS1	97
LRRK2	98
CRTC1	99
GLP1R	100

SUPPLEMENTARY DATA

Supplementary Table 5. Significantly enriched reactome pathways for 71 aging-specific high-confidence targets

ID	Description	GeneRatio	pvalue	p.adjust	geneID	Count
R-HSA-449147	Signaling by Interleukins	0.371428571	4.10E-18	3.03E-15	PTPN11/SOD1/VEGFA/NFKB2/FOXO1/CDKN1A/FOXO3/MYC/CREB1/APP/NFKB1A/JUN/IRS1/IKBKB/SHC1/MAPK9/PIK3R1/MAPK14/CD42/PIK3CA/IL7R/LMNB1/HMGB1/S100B/MIF/GRB2	26
R-HSA-5663202	Diseases of signal transduction by growth factor receptors and second messengers	0.3	1.73E-13	6.39E-11	PTPN11/FOXO1/CDKN1A/EGF/FOXO3/MYC/CREB1/KL/IRS1/LMNA/MDM2/SHC1/HDAC3/PSEN1/PIK3R1/CTNNB1/PIK3CA/HDAC2/CEBPB/NCOR2/GRB2	21
R-HSA-2219528	PI3K/AKT Signaling in Cancer	0.171428571	2.18E-12	5.36E-10	PTPN11/FOXO1/CDKN1A/EGF/FOXO3/CREB1/KL/IRS1/MDM2/PIK3R1/PIK3CA/GRB2	12
R-HSA-201556	Signaling by ALK	0.114285714	4.09E-12	7.55E-10	MYC/IRS1/SHC1/HDAC3/PIK3R1/PIK3CA/HDAC2/SIN3A	8
R-HSA-1257604	PIP3 activates AKT signaling	0.228571429	8.58E-12	1.27E-09	PTPN11/FOXO1/CDKN1A/EGF/FOXO3/CREB1/KL/JUN/IRS1/MDM2/HDAC3/PIK3R1/PIK3CA/HDAC2/EGR1/GRB2	16
R-HSA-166166	MyD88-independent TLR4 cascade	0.157142857	7.73E-11	7.20E-09	PTPN11/NFKB2/CREB1/APP/NFKB1A/JUN/IKBKB/MAPK9/MAPK14/HMGB1/S100B	11
R-HSA-937061	TRIF(TICAM1)-mediated TLR4 signaling	0.157142857	7.73E-11	7.20E-09	PTPN11/NFKB2/CREB1/APP/NFKB1A/JUN/IKBKB/MAPK9/MAPK14/HMGB1/S100B	11
R-HSA-9006925	Intracellular signaling by second messengers	0.228571429	7.80E-11	7.20E-09	PTPN11/FOXO1/CDKN1A/EGF/FOXO3/CREB1/KL/JUN/IRS1/MDM2/HDAC3/PIK3R1/PIK3CA/HDAC2/EGR1/GRB2	16
R-HSA-2559583	Cellular Senescence	0.185714286	2.74E-10	2.24E-08	CDKN2A/CDKN1A/JUN/MDM2/CCNA2/MAPK9/SP1/E2F1/MAPK14/CDKN2B/LMNB1/ATM/CEBPB	13
R-HSA-168142	Toll Like Receptor 10 (TLR10) Cascade	0.142857143	4.80E-10	2.95E-08	NFKB2/CREB1/APP/NFKB1A/JUN/IKBKB/MAPK9/MAPK14/HMGB1/S100B	10
R-HSA-168176	Toll Like Receptor 5 (TLR5) Cascade	0.142857143	4.80E-10	2.95E-08	NFKB2/CREB1/APP/NFKB1A/JUN/IKBKB/MAPK9/MAPK14/HMGB1/S100B	10
R-HSA-975871	MyD88 cascade initiated on plasma membrane	0.142857143	4.80E-10	2.95E-08	NFKB2/CREB1/APP/NFKB1A/JUN/IKBKB/MAPK9/MAPK14/HMGB1/S100B	10
R-HSA-9034015	Signaling by NTRK3 (TRKC)	0.085714286	6.89E-10	3.91E-08	IRS1/SHC1/PIK3R1/PIK3CA/BAX/GRB2	6

SUPPLEMENTARY DATA

R-HSA-975138	TRAF6 mediated induction of NFκB and MAP kinases upon TLR7/8 or 9 activation	0.142857143	7.96E-10	4.20E-08	NFKB2/CREB1/APP/NFKBIA/JUN/IKBKB/MAPK9/MAPK14/HMGB1/S100B	10
R-HSA-975155	MyD88 dependent cascade initiated on endosome	0.142857143	8.78E-10	4.32E-08	NFKB2/CREB1/APP/NFKBIA/JUN/IKBKB/MAPK9/MAPK14/HMGB1/S100B	10
R-HSA-168181	Toll Like Receptor 7/8 (TLR7/8) Cascade	0.142857143	9.68E-10	4.46E-08	NFKB2/CREB1/APP/NFKBIA/JUN/IKBKB/MAPK9/MAPK14/HMGB1/S100B	10
R-HSA-168164	Toll Like Receptor 3 (TLR3) Cascade	0.142857143	1.07E-09	4.63E-08	NFKB2/CREB1/APP/NFKBIA/JUN/IKBKB/MAPK9/MAPK14/HMGB1/S100B	10
R-HSA-168138	Toll Like Receptor 9 (TLR9) Cascade	0.142857143	1.29E-09	5.28E-08	NFKB2/CREB1/APP/NFKBIA/JUN/IKBKB/MAPK9/MAPK14/HMGB1/S100B	10
R-HSA-5683057	MAPK family signaling cascades	0.214285714	1.64E-09	6.38E-08	PTPN11/FOXO1/EGF/FOXO3/MYC/CDK1/KL/JUN/IRS1/SHC1/PIK3R1/CDC42/PIK3CA/PTK2/GRB2	15
R-HSA-166016	Toll Like Receptor 4 (TLR4) Cascade	0.157142857	1.75E-09	6.44E-08	PTPN11/NFKB2/CREB1/APP/NFKBIA/JUN/IKBKB/MAPK9/MAPK14/HMGB1/S100B	11
R-HSA-166058	MyD88:MAL(TIRAP) cascade initiated on plasma membrane	0.142857143	2.22E-09	7.44E-08	NFKB2/CREB1/APP/NFKBIA/JUN/IKBKB/MAPK9/MAPK14/HMGB1/S100B	10
R-HSA-168188	Toll Like Receptor TLR6:TLR2 Cascade	0.142857143	2.22E-09	7.44E-08	NFKB2/CREB1/APP/NFKBIA/JUN/IKBKB/MAPK9/MAPK14/HMGB1/S100B	10
R-HSA-168179	Toll Like Receptor TLR1:TLR2 Cascade	0.142857143	2.88E-09	8.85E-08	NFKB2/CREB1/APP/NFKBIA/JUN/IKBKB/MAPK9/MAPK14/HMGB1/S100B	10
R-HSA-181438	Toll Like Receptor 2 (TLR2) Cascade	0.142857143	2.88E-09	8.85E-08	NFKB2/CREB1/APP/NFKBIA/JUN/IKBKB/MAPK9/MAPK14/HMGB1/S100B	10
R-HSA-1236394	Signaling by ERBB4	0.114285714	3.02E-09	8.90E-08	EGF/APOE/SHC1/PSEN1/PIK3R1/PIK3CA/S100B/GRB2	8
R-HSA-3700989	Transcriptional Regulation by TP53	0.214285714	6.42E-09	1.82E-07	CDKN2A/BLM/CDKN1A/WRN/CDK1/JUN/MDM2/CCNA2/PCNA/E2F1/MAPK14/PTEN/ATM/HDAC2/BAX	15
R-HSA-168898	Toll-like Receptor Cascades	0.157142857	7.87E-09	2.15E-07	PTPN11/NFKB2/CREB1/APP/NFKBIA/JUN/IKBKB/MAPK9/MAPK14/HMGB1/S100B	11
R-HSA-933542	TRAF6 mediated NF-κB activation	0.085714286	9.47E-09	2.41E-07	NFKB2/APP/NFKBIA/IKBKB/HMGB1/S100B	6
R-HSA-9734009	Defective Intrinsic Pathway for Apoptosis	0.085714286	9.47E-09	2.41E-07	CDKN2A/FOXO3/APP/JUN/LMNA/LMNB1	6
R-HSA-166520	Signaling by NTRKs	0.142857143	1.28E-08	3.14E-07	PTPN11/CREB1/IRS1/SHC1/PIK3R1/MAPK14/PIK3CA/BAX/EGR1/GRB2	10
R-HSA-3108232	SUMO E3 ligases SUMOylate target proteins	0.157142857	1.95E-08	4.63E-07	CDKN2A/NFKB2/BLM/WRN/NFKBIA/MDM2/PCNA/TP	11

SUPPLEMENTARY DATA

					53BP1/HDAC2/NCOR2/SIN3A	
R-HSA-9615017	FOXO-mediated transcription of oxidative stress, metabolic and neuronal genes	0.085714286	2.49E-08	5.74E-07	FOXO1/FOXO3/CAT/HDAC2/SIN3A/SIRT3	6
R-HSA-2990846	SUMOylation	0.157142857	2.73E-08	5.74E-07	CDKN2A/NFKB2/BLM/WRN/NFKBIA/MDM2/PCNA/TP53BP1/HDAC2/NCOR2/SIN3A	11
R-HSA-177929	Signaling by EGFR	0.1	2.80E-08	5.74E-07	PTPN11/EGF/SHC1/PIK3R1/CDC42/PIK3CA/GRB2	7
R-HSA-5637810	Constitutive Signaling by EGFRvIII	0.071428571	2.80E-08	5.74E-07	EGF/SHC1/PIK3R1/PIK3CA/GRB2	5
R-HSA-5637812	Signaling by EGFRvIII in Cancer	0.071428571	2.80E-08	5.74E-07	EGF/SHC1/PIK3R1/PIK3CA/GRB2	5
R-HSA-5654687	Downstream signaling of activated FGFR1	0.085714286	3.82E-08	7.62E-07	PTPN11/KL/SHC1/PIK3R1/PIK3CA/GRB2	6
R-HSA-9665348	Signaling by ERBB2 ECD mutants	0.071428571	4.05E-08	7.67E-07	EGF/SHC1/PIK3R1/PIK3CA/GRB2	5
R-HSA-9703648	Signaling by FLT3 ITD and TKD mutants	0.071428571	4.05E-08	7.67E-07	PTPN11/CDKN1A/PIK3R1/PIK3CA/GRB2	5
R-HSA-2428924	IGF1R signaling cascade	0.1	4.25E-08	7.84E-07	PTPN11/KL/IRS1/SHC1/PIK3R1/PIK3CA/GRB2	7
R-HSA-9006931	Signaling by Nuclear Receptors	0.185714286	4.51E-08	8.11E-07	EGF/FOXO3/MYC/CREB1/JUN/APOE/SHC1/HDAC3/SP1/PIK3R1/PIK3CA/PTK2/NCOR2	13
R-HSA-2404192	Signaling by Type 1 Insulin-like Growth Factor 1 Receptor (IGF1R)	0.1	4.86E-08	8.33E-07	PTPN11/KL/IRS1/SHC1/PIK3R1/PIK3CA/GRB2	7
R-HSA-74751	Insulin receptor signalling cascade	0.1	4.86E-08	8.33E-07	PTPN11/KL/IRS1/SHC1/PIK3R1/PIK3CA/GRB2	7
R-HSA-180292	GAB1 signalosome	0.071428571	5.71E-08	9.58E-07	PTPN11/EGF/PIK3R1/PIK3CA/GRB2	5
R-HSA-5633007	Regulation of TP53 Activity	0.142857143	6.98E-08	1.15E-06	CDKN2A/BLM/WRN/CDK1/MDM2/CCNA2/MAPK14/PIK3R1/ATM/HDAC2	10
R-HSA-210993	Tie2 Signaling	0.071428571	7.87E-08	1.26E-06	PTPN11/SHC1/PIK3R1/PIK3CA/GRB2	5
R-HSA-76002	Platelet activation, signaling and aggregation	0.171428571	1.01E-07	1.58E-06	PTPN11/SOD1/VEGFA/EGF/APP/SHC1/PIK3R1/MAPK14/CDC42/PIK3CA/PTK2/GRB2	12
R-HSA-1236382	Constitutive Signaling by Ligand-Responsive EGFR Cancer Variants	0.071428571	1.06E-07	1.60E-06	EGF/SHC1/PIK3R1/PIK3CA/GRB2	5
R-HSA-5637815	Signaling by Ligand-Responsive EGFR Variants in Cancer	0.071428571	1.06E-07	1.60E-06	EGF/SHC1/PIK3R1/PIK3CA/GRB2	5

SUPPLEMENTARY DATA

R-HSA-5693567	HDR through Homologous Recombination (HRR) or Single Strand Annealing (SSA)	0.128571429	1.48E-07	2.18E-06	BLM/WRN/ERCC1/CCNA2/SIRT6/PCNA/TP53BP1/ABL1/ATM	9
R-HSA-9614085	FOXO-mediated transcription	0.1	1.80E-07	2.61E-06	FOXO1/CDKN1A/FOXO3/CAT/HDAC2/SIN3A/SIRT3	7
R-HSA-5654689	PI-3K cascade:FGFR1	0.071428571	1.84E-07	2.61E-06	PTPN11/KL/PIK3R1/PIK3CA/GRB2	5
R-HSA-5693538	Homology Directed Repair	0.128571429	2.17E-07	3.02E-06	BLM/WRN/ERCC1/CCNA2/SIRT6/PCNA/TP53BP1/ABL1/ATM	9
R-HSA-8862803	Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models	0.071428571	2.37E-07	3.18E-06	FOXO3/APP/JUN/LMNA/LMNB1	5
R-HSA-8863678	Neurodegenerative Diseases	0.071428571	2.37E-07	3.18E-06	FOXO3/APP/JUN/LMNA/LMNB1	5
R-HSA-109704	PI3K Cascade	0.085714286	3.43E-07	4.44E-06	PTPN11/KL/IRS1/PIK3R1/PIK3CA/GRB2	6
R-HSA-445989	TAK1-dependent IKK and NF-kappa-B activation	0.085714286	3.43E-07	4.44E-06	NFKB2/APP/NFKBIA/IKBKB/HMGB1/S100B	6
R-HSA-453279	Mitotic G1 phase and G1/S transition	0.128571429	4.45E-07	5.52E-06	CDKN2A/CDKN1A/MYC/CDK1/CCNA2/PCNA/E2F1/CDKN2B/ABL1	9
R-HSA-1643713	Signaling by EGFR in Cancer	0.071428571	4.71E-07	5.52E-06	EGF/SHC1/PIK3R1/PIK3CA/GRB2	5
R-HSA-5654708	Downstream signaling of activated FGFR3	0.071428571	4.71E-07	5.52E-06	PTPN11/SHC1/PIK3R1/PIK3CA/GRB2	5
R-HSA-5674400	Constitutive Signaling by AKT1 E17K in Cancer	0.071428571	4.71E-07	5.52E-06	FOXO1/CDKN1A/FOXO3/CREB1/MDM2	5
R-HSA-9006115	Signaling by NTRK2 (TRKB)	0.071428571	4.71E-07	5.52E-06	PTPN11/SHC1/PIK3R1/PIK3CA/GRB2	5
R-HSA-9664565	Signaling by ERBB2 KD Mutants	0.071428571	4.71E-07	5.52E-06	EGF/SHC1/PIK3R1/PIK3CA/GRB2	5
R-HSA-6791312	TP53 Regulates Transcription of Cell Cycle Genes	0.085714286	5.14E-07	5.92E-06	CDKN1A/CDK1/CCNA2/PCNA/E2F1/BAX	6
R-HSA-1227990	Signaling by ERBB2 in Cancer	0.071428571	5.80E-07	6.46E-06	EGF/SHC1/PIK3R1/PIK3CA/GRB2	5
R-HSA-112399	IRS-mediated signalling	0.085714286	5.84E-07	6.46E-06	PTPN11/KL/IRS1/PIK3R1/PIK3CA/GRB2	6
R-HSA-9009391	Extra-nuclear estrogen signaling	0.1	5.86E-07	6.46E-06	EGF/FOXO3/CREB1/SHC1/PIK3R1/PIK3CA/PTK2	7
R-HSA-2219530	Constitutive Signaling by Aberrant PI3K in Cancer	0.1	6.41E-07	6.95E-06	PTPN11/EGF/KL/IRS1/PIK3R1/PIK3CA/GRB2	7
R-HSA-187037	Signaling by NTRK1 (TRKA)	0.114285714	6.95E-07	7.26E-06	CREB1/IRS1/SHC1/PIK3R1/MAPK14/PIK3CA/EGR1/GRB2	8

SUPPLEMENTARY DATA

R-HSA-74752	Signaling by Insulin receptor	0.1	7.00E-07	7.26E-06	PTPN11/KL/IRS1/SHC1/PIK3R1/PIK3CA/GRB2	7
R-HSA-1538133	G0 and Early G1	0.071428571	7.09E-07	7.26E-06	MYC/CDK1/CCNA2/PCNA/E2F1	5
R-HSA-5654716	Downstream signaling of activated FGFR4	0.071428571	7.09E-07	7.26E-06	PTPN11/SHC1/PIK3R1/PIK3CA/GRB2	5
R-HSA-5654736	Signaling by FGFR1	0.085714286	7.49E-07	7.57E-06	PTPN11/KL/SHC1/PIK3R1/PIK3CA/GRB2	6
R-HSA-9682385	FLT3 signaling in disease	0.071428571	8.58E-07	8.56E-06	PTPN11/CDKN1A/PIK3R1/PIK3CA/GRB2	5
R-HSA-168928	DDX58/IFIH1-mediated induction of interferon-alpha/beta	0.1	9.04E-07	8.89E-06	NFKB2/APP/NFKBIA/IKKBK/PIN1/HMGB1/S100B	7
R-HSA-2428928	IRS-related events triggered by IGF1R	0.085714286	9.49E-07	9.10E-06	PTPN11/KL/IRS1/PIK3R1/PIK3CA/GRB2	6
R-HSA-75153	Apoptotic execution phase	0.085714286	9.49E-07	9.10E-06	LMNA/CTNNB1/LMNB1/HMGB1/PTK2/MAPT	6
R-HSA-9658195	Leishmania infection	0.128571429	9.99E-07	9.45E-06	NFKB2/CREB1/APP/JUN/MAPK14/CDC42/ABL1/PTK2/GRB2	9
R-HSA-5693532	DNA Double-Strand Break Repair	0.128571429	1.16E-06	1.09E-05	BLM/WRN/ERCC1/CCNA2/SIRT6/PCNA/TP53BP1/ABL1/ATM	9
R-HSA-5654696	Downstream signaling of activated FGFR2	0.071428571	1.23E-06	1.14E-05	PTPN11/SHC1/PIK3R1/PIK3CA/GRB2	5
R-HSA-9700206	Signaling by ALK in cancer	0.085714286	1.33E-06	1.20E-05	IRS1/SHC1/PIK3R1/PIK3CA/CEBPB/GRB2	6
R-HSA-9725370	Signaling by ALK fusions and activated point mutants	0.085714286	1.33E-06	1.20E-05	IRS1/SHC1/PIK3R1/PIK3CA/CEBPB/GRB2	6
R-HSA-8939211	ESR-mediated signaling	0.142857143	1.46E-06	1.30E-05	EGF/FOXO3/MYC/CREB1/JUN/SHC1/SP1/PIK3R1/PIK3CA/PTK2	10
R-HSA-6804756	Regulation of TP53 Activity through Phosphorylation	0.1	1.98E-06	1.73E-05	BLM/WRN/MDM2/CCNA2/MAPK14/PIN1/ATM	7
R-HSA-2559585	Oncogene Induced Senescence	0.071428571	2.02E-06	1.73E-05	CDKN2A/MDM2/SP1/E2F1/CDKN2B	5
R-HSA-9022692	Regulation of MECP2 expression and activity	0.071428571	2.02E-06	1.73E-05	CREB1/HDAC3/HDAC2/NCOR2/SIN3A	5
R-HSA-109581	Apoptosis	0.128571429	2.07E-06	1.76E-05	CDKN2A/LMNA/E2F1/CTNNB1/LMNB1/HMGB1/BAX/PTK2/MAPT	9
R-HSA-2454202	Fc epsilon receptor (FCERI) signaling	0.114285714	2.10E-06	1.76E-05	NFKBIA/JUN/IKKBK/SHC1/MAPK9/PIK3R1/PIK3CA/GRB2	8
R-HSA-157118	Signaling by NOTCH	0.142857143	2.44E-06	2.03E-05	EGF/MYC/CREB1/JUN/SIRT6/HDAC3/PSEN1/E2F1/HDAC2/NCOR2	10
R-HSA-1963642	PI3K events in ERBB2 signaling	0.057142857	2.76E-06	2.24E-05	EGF/PIK3R1/PIK3CA/GRB2	4

SUPPLEMENTARY DATA

R-HSA-2730905	Role of LAT2/NTAL/LAB on calcium mobilization	0.057142857	2.76E-06	2.24E-05	SHC1/PIK3R1/PIK3CA/GRB2	4
R-HSA-6804757	Regulation of TP53 Degradation	0.071428571	3.16E-06	2.54E-05	CDKN2A/CDK1/MDM2/CCNA2/ATM	5
R-HSA-4420097	VEGFA-VEGFR2 Pathway	0.1	3.24E-06	2.57E-05	VEGFA/PIK3R1/MAPK14/CTNNB1/CDC42/PIK3CA/PTK2	7
R-HSA-5685938	HDR through Single Strand Annealing (SSA)	0.071428571	3.64E-06	2.83E-05	BLM/WRN/ERCC1/ABL1/ATM	5
R-HSA-6806003	Regulation of TP53 Expression and Degradation	0.071428571	3.64E-06	2.83E-05	CDKN2A/CDK1/MDM2/CCNA2/ATM	5
R-HSA-111465	Apoptotic cleavage of cellular proteins	0.071428571	4.17E-06	3.17E-05	LMNA/CTNNB1/LMNB1/PTK2/MAPT	5
R-HSA-9607240	FLT3 Signaling	0.071428571	4.17E-06	3.17E-05	PTPN11/FOXO3/PIK3R1/PIK3CA/GRB2	5
R-HSA-5654710	PI-3K cascade:FGFR3	0.057142857	4.59E-06	3.46E-05	PTPN11/PIK3R1/PIK3CA/GRB2	4
R-HSA-6811558	PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling	0.1	5.12E-06	3.82E-05	PTPN11/EGF/KL/IRS1/PIK3R1/PIK3CA/GRB2	7
R-HSA-5654741	Signaling by FGFR3	0.071428571	5.41E-06	3.95E-05	PTPN11/SHC1/PIK3R1/PIK3CA/GRB2	5
R-HSA-8853659	RET signaling	0.071428571	5.41E-06	3.95E-05	PTPN11/SHC1/PIK3R1/PIK3CA/GRB2	5
R-HSA-9703465	Signaling by FLT3 fusion proteins	0.057142857	5.79E-06	4.16E-05	CDKN1A/PIK3R1/PIK3CA/GRB2	4
R-HSA-194138	Signaling by VEGF	0.1	5.80E-06	4.16E-05	VEGFA/PIK3R1/MAPK14/CTNNB1/CDC42/PIK3CA/PTK2	7
R-HSA-5654743	Signaling by FGFR4	0.071428571	6.13E-06	4.35E-05	PTPN11/SHC1/PIK3R1/PIK3CA/GRB2	5
R-HSA-5357801	Programmed Cell Death	0.128571429	7.11E-06	4.99E-05	CDKN2A/LMNA/E2F1/CTNNB1/LMNB1/HMGB1/BAX/PTK2/MAPT	9
R-HSA-5654720	PI-3K cascade:FGFR4	0.057142857	7.20E-06	5.01E-05	PTPN11/PIK3R1/PIK3CA/GRB2	4
R-HSA-199418	Negative regulation of the PI3K/AKT network	0.1	7.83E-06	5.40E-05	PTPN11/EGF/KL/IRS1/PIK3R1/PIK3CA/GRB2	7
R-HSA-6806834	Signaling by MET	0.085714286	1.13E-05	7.72E-05	PTPN11/SHC1/PIK3R1/PIK3CA/PTK2/GRB2	6
R-HSA-69231	Cyclin D associated events in G1	0.071428571	1.22E-05	8.17E-05	CDKN2A/CDKN1A/E2F1/CDKN2B/ABL1	5
R-HSA-69236	G1 Phase	0.071428571	1.22E-05	8.17E-05	CDKN2A/CDKN1A/E2F1/CDKN2B/ABL1	5
R-HSA-5654695	PI-3K cascade:FGFR2	0.057142857	1.30E-05	8.62E-05	PTPN11/PIK3R1/PIK3CA/GRB2	4
R-HSA-5684996	MAPK1/MAPK3 signaling	0.142857143	1.35E-05	8.84E-05	PTPN11/EGF/CDK1/KL/IRS1/SHC1/PIK3R1/PIK3CA/PTK2/GRB2	10
R-HSA-512988	Interleukin-3, Interleukin-5 and GM-CSF signaling	0.071428571	1.35E-05	8.84E-05	PTPN11/SHC1/PIK3R1/PIK3CA/GRB2	5

SUPPLEMENTARY DATA

R-HSA-2559580	Oxidative Stress Induced Senescence	0.1	1.37E-05	8.86E-05	CDKN2A/JUN/MDM2/MAPK9/E2F1/MAPK14/CDKN2B	7
R-HSA-9634638	Estrogen-dependent nuclear events downstream of ESR-membrane signaling	0.057142857	1.55E-05	9.93E-05	EGF/FOXO3/CREB1/PTK2	4
R-HSA-69620	Cell Cycle Checkpoints	0.142857143	1.57E-05	9.98E-05	CDKN2A/BLM/CDKN1A/WRN/CDK1/MDM2/CCNA2/TP53BP1/ATM/BUB1B	10
R-HSA-1227986	Signaling by ERBB2	0.071428571	1.66E-05	0.000104547	EGF/SHC1/PIK3R1/PIK3CA/GRB2	5
R-HSA-180786	Extension of Telomeres	0.071428571	1.83E-05	0.000113462	BLM/WRN/TERT/CCNA2/PNA	5
R-HSA-9006335	Signaling by Erythropoietin	0.057142857	1.83E-05	0.000113462	SHC1/PIK3R1/PIK3CA/GRB2	4
R-HSA-2029480	Fcγ receptor (FCGR) dependent phagocytosis	0.085714286	1.84E-05	0.000113462	PIK3R1/CDC42/PIK3CA/ABL1/PTK2/GRB2	6
R-HSA-190236	Signaling by FGFR	0.085714286	1.97E-05	0.000120248	PTPN11/KL/SHC1/PIK3R1/PIK3CA/GRB2	6
R-HSA-5687128	MAPK6/MAPK4 signaling	0.085714286	2.25E-05	0.000134751	FOXO1/FOXO3/MYC/CDK1/JUN/CDC42	6
R-HSA-9616222	Transcriptional regulation of granulopoiesis	0.085714286	2.25E-05	0.000134751	CDKN1A/MYC/CREB1/E2F1/CEBPA/CEBPB	6
R-HSA-912526	Interleukin receptor SHC signaling	0.057142857	2.52E-05	0.000149956	SHC1/PIK3R1/PIK3CA/GRB2	4
R-HSA-450341	Activation of the AP-1 family of transcription factors	0.042857143	3.01E-05	0.000171186	JUN/MAPK9/MAPK14	3
R-HSA-74749	Signal attenuation	0.042857143	3.01E-05	0.000171186	IRS1/SHC1/GRB2	3
R-HSA-9617629	Regulation of FOXO transcriptional activity by acetylation	0.042857143	3.01E-05	0.000171186	FOXO1/FOXO3/SIRT3	3
R-HSA-9701898	STAT3 nuclear events downstream of ALK signaling	0.042857143	3.01E-05	0.000171186	HDAC3/HDAC2/SIN3A	3
R-HSA-9702518	STAT5 activation downstream of FLT3 ITD mutants	0.042857143	3.01E-05	0.000171186	PTPN11/CDKN1A/GRB2	3
R-HSA-9711123	Cellular response to chemical stress	0.114285714	3.02E-05	0.000171186	CDKN2A/SOD1/MYC/CAT/HDAC3/NFE2L2/NCOR2/SIN3A	8
R-HSA-186763	Downstream signal transduction	0.057142857	3.38E-05	0.000182279	PTPN11/PIK3R1/PIK3CA/GRB2	4
R-HSA-2424491	DAP12 signaling	0.057142857	3.38E-05	0.000182279	SHC1/PIK3R1/PIK3CA/GRB2	4
R-HSA-525793	Myogenesis	0.057142857	3.38E-05	0.000182279	MAPK14/CTNBN1/CDC42/ABL1	4
R-HSA-2644602	Signaling by NOTCH1 PEST Domain Mutants in Cancer	0.071428571	3.44E-05	0.000182279	MYC/HDAC3/PSEN1/HDAC2/NCOR2	5
R-HSA-2644603	Signaling by NOTCH1 in Cancer	0.071428571	3.44E-05	0.000182279	MYC/HDAC3/PSEN1/HDAC2/NCOR2	5

SUPPLEMENTARY DATA

R-HSA-2644606	Constitutive Signaling by NOTCH1 PEST Domain Mutants	0.071428571	3.44E-05	0.000182279	MYC/HDAC3/PSEN1/HDAC2/NCOR2	5
R-HSA-2894858	Signaling by NOTCH1 HD+PEST Domain Mutants in Cancer	0.071428571	3.44E-05	0.000182279	MYC/HDAC3/PSEN1/HDAC2/NCOR2	5
R-HSA-2894862	Constitutive Signaling by NOTCH1 HD+PEST Domain Mutants	0.071428571	3.44E-05	0.000182279	MYC/HDAC3/PSEN1/HDAC2/NCOR2	5
R-HSA-5693607	Processing of DNA double-strand break ends	0.085714286	3.46E-05	0.000182279	BLM/WRN/CCNA2/SIRT6/TP53BP1/ATM	6
R-HSA-8878159	Transcriptional regulation by RUNX3	0.085714286	3.46E-05	0.000182279	CDKN2A/CDKN1A/FOXO3/MYC/MDM2/CTNNB1	6
R-HSA-5655291	Signaling by FGFR4 in disease	0.042857143	4.12E-05	0.0002158	PIK3R1/PIK3CA/GRB2	3
R-HSA-450282	MAPK targets/ Nuclear events mediated by MAP kinases	0.057142857	4.43E-05	0.000227038	CREB1/JUN/MAPK9/MAPK14	4
R-HSA-5260271	Diseases of Immune System	0.057142857	4.43E-05	0.000227038	NFKB2/NFKBIA/IKBKB/HMGB1	4
R-HSA-5602358	Diseases associated with the TLR signaling cascade	0.057142857	4.43E-05	0.000227038	NFKB2/NFKBIA/IKBKB/HMGB1	4
R-HSA-8986944	Transcriptional Regulation by MECP2	0.071428571	4.77E-05	0.000242629	CREB1/HDAC3/HDAC2/NCOR2/SIN3A	5
R-HSA-2871796	FCERI mediated MAPK activation	0.057142857	5.04E-05	0.000254673	JUN/SHC1/MAPK9/GRB2	4
R-HSA-73894	DNA Repair	0.142857143	5.12E-05	0.000256915	BLM/WRN/ERCC1/CCNA2/SIRT6/PCNA/TP53BP1/ABL1/ATM/XPA	10
R-HSA-450294	MAP kinase activation	0.071428571	5.15E-05	0.000256915	CREB1/JUN/IKBKB/MAPK9/MAPK14	5
R-HSA-446652	Interleukin-1 family signaling	0.1	5.37E-05	0.000265673	PTPN11/NFKB2/APP/NFKBIA/IKBKB/HMGB1/S100B	7
R-HSA-9645723	Diseases of programmed cell death	0.085714286	5.43E-05	0.000265673	CDKN2A/FOXO3/APP/JUN/LMNA/LMNB1	6
R-HSA-9673767	Signaling by PDGFRA transmembrane, juxtamembrane and kinase domain mutants	0.042857143	5.47E-05	0.000265673	PIK3R1/PIK3CA/GRB2	3
R-HSA-9673770	Signaling by PDGFRA extracellular domain mutants	0.042857143	5.47E-05	0.000265673	PIK3R1/PIK3CA/GRB2	3
R-HSA-389356	CD28 co-stimulation	0.057142857	5.71E-05	0.000275196	PIK3R1/CDC42/PIK3CA/GRB2	4

SUPPLEMENTARY DATA

R-HSA-69563	p53-Dependent G1 DNA Damage Response	0.071428571	6.45E-05	0.000307262	CDKN2A/CDKN1A/MDM2/CCNA2/ATM	5
R-HSA-69580	p53-Dependent G1/S DNA damage checkpoint	0.071428571	6.45E-05	0.000307262	CDKN2A/CDKN1A/MDM2/CCNA2/ATM	5
R-HSA-6785807	Interleukin-4 and Interleukin-13 signaling	0.085714286	6.72E-05	0.000317727	VEGFA/FOXO1/CDKN1A/FOXO3/MYC/PIK3R1	6
R-HSA-879415	Advanced glycosylation endproduct receptor signaling	0.042857143	7.08E-05	0.000332826	APP/HMGB1/S100B	3
R-HSA-114604	GPVI-mediated activation cascade	0.057142857	7.23E-05	0.000337681	PTPN11/PIK3R1/CDC42/PIK3CA	4
R-HSA-69615	G1/S DNA Damage Checkpoints	0.071428571	7.45E-05	0.000345902	CDKN2A/CDKN1A/MDM2/CCNA2/ATM	5
R-HSA-2559582	Senescence-Associated Secretory Phenotype (SASP)	0.085714286	7.83E-05	0.000361025	CDKN2A/CDKN1A/JUN/CCNA2/CDKN2B/CEBPB	6
R-HSA-388841	Costimulation by the CD28 family	0.071428571	7.99E-05	0.000366456	PTPN11/PIK3R1/CDC42/PIK3CA/GRB2	5
R-HSA-5663213	RHO GTPases Activate WASPs and WAVEs	0.057142857	8.09E-05	0.00036871	CDC42/ABL1/PTK2/GRB2	4
R-HSA-180336	SHC1 events in EGFR signaling	0.042857143	8.97E-05	0.000394027	EGF/SHC1/GRB2	3
R-HSA-6804116	TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest	0.042857143	8.97E-05	0.000394027	CDKN1A/CCNA2/E2F1	3
R-HSA-9005891	Loss of function of MECP2 in Rett syndrome	0.042857143	8.97E-05	0.000394027	HDAC3/NCOR2/SIN3A	3
R-HSA-9005895	Pervasive developmental disorders	0.042857143	8.97E-05	0.000394027	HDAC3/NCOR2/SIN3A	3
R-HSA-9675151	Disorders of Developmental Biology	0.042857143	8.97E-05	0.000394027	HDAC3/NCOR2/SIN3A	3
R-HSA-9697154	Disorders of Nervous System Development	0.042857143	8.97E-05	0.000394027	HDAC3/NCOR2/SIN3A	3
R-HSA-9020702	Interleukin-1 signaling	0.085714286	9.08E-05	0.000396511	NFKB2/APP/NFKBIA/IKBKB/HMGB1/S100B	6
R-HSA-448424	Interleukin-17 signaling	0.071428571	9.17E-05	0.000398068	CREB1/JUN/IKBKB/MAPK9/MAPK14	5
R-HSA-8864260	Transcriptional regulation by the AP-2 (TFAP2) family of transcription factors	0.057142857	0.00010439	0.000430955	VEGFA/CDKN1A/MYC/APOE	4
R-HSA-8950505	Gene and protein expression by JAK-STAT signaling after Interleukin-12 stimulation	0.057142857	0.00010439	0.000430955	SOD1/CDC42/LMN1/MIF	4

SUPPLEMENTARY DATA

R-HSA-5654738	Signaling by FGFR2	0.071428571	0.00010 4732	0.0004467 77	PTPN11/SHC1/PIK3R1/PIK3 CA/GRB2	5
R-HSA-4419969	Depolymerisation of the Nuclear Lamina	0.042857143	0.00011 1602	0.0004713 15	CDK1/LMNA/LMN1	3
R-HSA-1980143	Signaling by NOTCH1	0.071428571	0.00011 1762	0.0004713 15	MYC/HDAC3/PSEN1/HDAC 2/NCOR2	5
R-HSA-1362300	Transcription of E2F targets under negative control by p107 (RBL1) and p130 (RBL2) in complex with HDAC1	0.042857143	0.00013 672	0.0005700 53	CDK1/CCNA2/E2F1	3
R-HSA-391160	Signal regulatory protein family interactions	0.042857143	0.00013 672	0.0005700 53	PTPN11/PTK2/GRB2	3
R-HSA-1433557	Signaling by SCF-KIT	0.057142857	0.00016 3883	0.0006737 75	PTPN11/PIK3R1/PIK3CA/G RB2	4
R-HSA-1810476	RIP-mediated NFkB activation via ZBP1	0.042857143	0.00016 5248	0.0006737 75	NFKB2/NFKBIA/IKBKB	3
R-HSA-9022699	MECP2 regulates neuronal receptors and channels	0.042857143	0.00016 5248	0.0006737 75	CREB1/HDAC2/SIN3A	3
R-HSA-9617828	FOXO-mediated transcription of cell cycle genes	0.042857143	0.00016 5248	0.0006737 75	FOXO1/CDKN1A/FOXO3	3
R-HSA-2172127	DAP12 interactions	0.057142857	0.00017 9396	0.0007199 19	SHC1/PIK3R1/PIK3CA/GRB 2	4
R-HSA-451927	Interleukin-2 family signaling	0.057142857	0.00017 9396	0.0007199 19	SHC1/PIK3R1/PIK3CA/GRB 2	4
R-HSA-1500931	Cell-Cell communication	0.085714286	0.00017 9492	0.0007199 19	PTPN11/PIK3R1/CTN1B/PI K3CA/PTK2/GRB2	6
R-HSA-69206	G1/S Transition	0.085714286	0.00019 5222	0.0007787 79	CDKN1A/MYC/CDK1/CCN A2/PCNA/E2F1	6
R-HSA-1839117	Signaling by cytosolic FGFR1 fusion mutants	0.042857143	0.00019 738	0.0007789 64	PIK3R1/PIK3CA/GRB2	3
R-HSA-6804114	TP53 Regulates Transcription of Genes Involved in G2 Cell Cycle Arrest	0.042857143	0.00019 738	0.0007789 64	CDK1/PCNA/BAX	3
R-HSA-9020591	Interleukin-12 signaling	0.057142857	0.00023 2294	0.0008967 61	SOD1/CDC42/LMN1/MIF	4
R-HSA-9707616	Heme signaling	0.057142857	0.00023 2294	0.0008967 61	CREB1/CLOCK/HDAC3/NF E2L2	4
R-HSA-1362277	Transcription of E2F targets under negative control by DREAM complex	0.042857143	0.00023 3304	0.0008967 61	MYC/PCNA/E2F1	3
R-HSA-174414	Processive synthesis on the C-strand of the telomere	0.042857143	0.00023 3304	0.0008967 61	BLM/WRN/PCNA	3
R-HSA-2995383	Initiation of Nuclear Envelope (NE) Reformation	0.042857143	0.00023 3304	0.0008967 61	CDK1/LMNA/LMN1	3

SUPPLEMENTARY DATA

R-HSA-202733	Cell surface interactions at the vascular wall	0.085714286	0.00024 9041	0.0009522 9	PTPN11/SHC1/PIK3R1/PIK3CA/MIF/GRB2	6
R-HSA-2122947	NOTCH1 Intracellular Domain Regulates Transcription	0.057142857	0.00025 2182	0.0009593 31	MYC/HDAC3/HDAC2/NCO R2	4
R-HSA-167044	Signalling to RAS	0.042857143	0.00027 3205	0.0010131 91	SHC1/MAPK14/GRB2	3
R-HSA-3232118	SUMOylation of transcription factors	0.042857143	0.00027 3205	0.0010131 91	CDKN2A/MDM2/TP53BP1	3
R-HSA-9669938	Signaling by KIT in disease	0.042857143	0.00027 3205	0.0010131 91	PIK3R1/PIK3CA/GRB2	3
R-HSA-9670439	Signaling by phosphorylated juxtamembrane, extracellular and kinase domain KIT mutants	0.042857143	0.00027 3205	0.0010131 91	PIK3R1/PIK3CA/GRB2	3
R-HSA-9671555	Signaling by PDGFR in disease	0.042857143	0.00027 3205	0.0010131 91	PIK3R1/PIK3CA/GRB2	3
R-HSA-373752	Netrin-1 signaling	0.057142857	0.00029 5586	0.0010907 14	PTPN11/MAPK14/CDC42/PT K2	4
R-HSA-1606322	ZBP1(DAI) mediated induction of type I IFNs	0.042857143	0.00031 7264	0.0011591 14	NFKB2/NFKBIA/IKBKB	3
R-HSA-5654688	SHC-mediated cascade:FGFR1	0.042857143	0.00031 7264	0.0011591 14	KL/SHC1/GRB2	3
R-HSA-2173793	Transcriptional activity of SMAD2/SMAD3:SMAD4 heterotrimer	0.057142857	0.00031 9187	0.0011603 93	MYC/SP1/CDKN2B/NCOR2	4
R-HSA-69473	G2/M DNA damage checkpoint	0.071428571	0.00032 7942	0.0011863 79	BLM/WRN/CDK1/TP53BP1/ATM	5
R-HSA-1250196	SHC1 events in ERBB2 signaling	0.042857143	0.00036 5659	0.0012973 87	EGF/SHC1/GRB2	3
R-HSA-5655332	Signaling by FGFR3 in disease	0.042857143	0.00036 5659	0.0012973 87	PIK3R1/PIK3CA/GRB2	3
R-HSA-912631	Regulation of signaling by CBL	0.042857143	0.00036 5659	0.0012973 87	PIK3R1/PIK3CA/GRB2	3
R-HSA-9665686	Signaling by ERBB2 TMD/JMD mutants	0.042857143	0.00036 5659	0.0012973 87	EGF/SHC1/GRB2	3
R-HSA-193704	p75 NTR receptor-mediated signalling	0.071428571	0.00039 8625	0.0014075 86	NFKBIA/IKBKB/HDAC3/PS EN1/HDAC2	5
R-HSA-5673001	RAF/MAP kinase cascade	0.114285714	0.00041 7529	0.0014639 81	EGF/KL/IRS1/SHC1/PIK3R1/PIK3CA/PTK2/GRB2	8
R-HSA-5654693	FRS-mediated FGFR1 signaling	0.042857143	0.00041 8564	0.0014639 81	PTPN11/KL/GRB2	3
R-HSA-168643	Nucleotide-binding domain, leucine rich repeat containing receptor (NLR) signaling pathways	0.057142857	0.00045 7859	0.0015938 66	NFKB2/APP/IKBKB/MAPK1 4	4
R-HSA-9709603	Impaired BRCA2 binding to PALB2	0.042857143	0.00047 6147	0.0016497 49	BLM/WRN/ATM	3

SUPPLEMENTARY DATA

R-HSA-447115	Interleukin-12 family signaling	0.057142857	0.00049 0027	0.0016899 06	SOD1/CDC42/LMN1/MIF	4
R-HSA-186797	Signaling by PDGF	0.057142857	0.00052 3774	0.0017978 86	PTPN11/PIK3R1/PIK3CA/GRB2	4
R-HSA-69273	Cyclin A/B1/B2 associated events during G2/M transition	0.042857143	0.00053 8575	0.0018066 76	CDK1/CCNA2/FOXM1	3
R-HSA-9701192	Defective HDR through Homologous Recombination (HRR) due to BRCA1 loss-of-function	0.042857143	0.00053 8575	0.0018066 76	BLM/WRN/ATM	3
R-HSA-9701193	Defective HDR through Homologous Recombination (HRR) due to PALB2 loss of function	0.042857143	0.00053 8575	0.0018066 76	BLM/WRN/ATM	3
R-HSA-9704331	Defective HDR through Homologous Recombination Repair (HRR) due to PALB2 loss of BRCA1 binding function	0.042857143	0.00053 8575	0.0018066 76	BLM/WRN/ATM	3
R-HSA-9704646	Defective HDR through Homologous Recombination Repair (HRR) due to PALB2 loss of BRCA2/RAD51/RA D51C binding function	0.042857143	0.00053 8575	0.0018066 76	BLM/WRN/ATM	3
R-HSA-9664407	Parasite infection	0.057142857	0.00055 9144	0.0018504 41	CDC42/ABL1/PTK2/GRB2	4
R-HSA-9664417	Leishmania phagocytosis	0.057142857	0.00055 9144	0.0018504 41	CDC42/ABL1/PTK2/GRB2	4
R-HSA-9664422	FCGR3A-mediated phagocytosis	0.057142857	0.00055 9144	0.0018504 41	CDC42/ABL1/PTK2/GRB2	4
R-HSA-8943724	Regulation of PTEN gene transcription	0.057142857	0.00059 618	0.0019642 01	JUN/HDAC3/HDAC2/EGR1	4
R-HSA-2029482	Regulation of actin dynamics for phagocytic cup formation	0.057142857	0.00063 4927	0.0020733 44	CDC42/ABL1/PTK2/GRB2	4
R-HSA-9707564	Cytoprotection by HMOX1	0.057142857	0.00063 4927	0.0020733 44	HDAC3/NFE2L2/NCOR2/SIN3A	4
R-HSA-354192	Integrin signaling	0.042857143	0.00067 8613	0.0021965 63	SHC1/PTK2/GRB2	3
R-HSA-5693554	Resolution of D-loop Structures through Synthesis-Dependent Strand Annealing (SDSA)	0.042857143	0.00067 8613	0.0021965 63	BLM/WRN/ATM	3
R-HSA-350054	Notch-HLH transcription pathway	0.042857143	0.00075 6536	0.0024274 95	HDAC3/HDAC2/NCOR2	3

SUPPLEMENTARY DATA

R-HSA-69205	G1/S-Specific Transcription	0.042857143	0.00075 6536	0.0024274 95	CDK1/PCNA/E2F1	3
R-HSA-1834949	Cytosolic sensors of pathogen-associated DNA	0.057142857	0.00076 1867	0.0024340 15	NFKB2/NFKBIA/IKBKB/CTNNB1	4
R-HSA-157579	Telomere Maintenance	0.071428571	0.00077 0023	0.0024494 7	BLM/WRN/TERT/CCNA2/P CNA	5
R-HSA-9674555	Signaling by CSF3 (G-CSF)	0.042857143	0.00092 8951	0.0029423 42	PTPN11/SHC1/GRB2	3
R-HSA-5685942	HDR through Homologous Recombination (HRR)	0.057142857	0.00095 7741	0.0030205 69	BLM/WRN/PCNA/ATM	4
R-HSA-400206	Regulation of lipid metabolism by PPARalpha	0.071428571	0.00097 4705	0.0030609 88	CLOCK/HDAC3/SP1/NCOR 2/SIN3A	5
R-HSA-182971	EGFR downregulation	0.042857143	0.00102 3735	0.0031878 32	EGF/CDC42/GRB2	3
R-HSA-1839124	FGFR1 mutant receptor activation	0.042857143	0.00102 3735	0.0031878 32	PIK3R1/PIK3CA/GRB2	3
R-HSA-8878166	Transcriptional regulation by RUNX2	0.071428571	0.00105 1175	0.0032595 27	CDKN1A/CDK1/HDAC3/AB L1/BAX	5
R-HSA-195258	RHO GTPase Effectors	0.114285714	0.00111 2428	0.0034350 3	MAPK14/CTNNB1/CDC42/P IN1/ABL1/PTK2/GRB2/BUB 1B	8
R-HSA-1251985	Nuclear signaling by ERBB4	0.042857143	0.00112 4426	0.0034576 11	APOE/PSEN1/S100B	3
R-HSA-5654726	Negative regulation of FGFR1 signaling	0.042857143	0.00123 1164	0.0037701 19	PTPN11/KL/GRB2	3
R-HSA-174417	Telomere C-strand (Lagging Strand) Synthesis	0.042857143	0.00134 4081	0.0040652 96	BLM/WRN/PCNA	3
R-HSA-187687	Signalling to ERKs	0.042857143	0.00134 4081	0.0040652 96	SHC1/MAPK14/GRB2	3
R-HSA-5693568	Resolution of D-loop Structures through Holliday Junction Intermediates	0.042857143	0.00134 4081	0.0040652 96	BLM/WRN/ATM	3
R-HSA-5693537	Resolution of D-Loop Structures	0.042857143	0.00146 3311	0.0043899 34	BLM/WRN/ATM	3
R-HSA-9709570	Impaired BRCA2 binding to RAD51	0.042857143	0.00146 3311	0.0043899 34	BLM/WRN/ATM	3
R-HSA-1266695	Interleukin-7 signaling	0.042857143	0.00158 8982	0.0047285 03	IRS1/PIK3R1/IL7R	3
R-HSA-2173796	SMAD2/SMAD3:SMAD4 heterotrimer regulates transcription	0.042857143	0.00158 8982	0.0047285 03	MYC/SP1/CDKN2B	3
R-HSA-2559586	DNA Damage/Telomere Stress Induced Senescence	0.057142857	0.00167 5241	0.0049651 72	CDKN1A/CCNA2/LMNB1/A TM	4
R-HSA-9029569	NR1H3 & NR1H2 regulate gene expression linked to cholesterol transport and efflux	0.042857143	0.00172 1218	0.0050810 36	APOE/HDAC3/NCOR2	3

SUPPLEMENTARY DATA

R-HSA-110056	MAPK3 (ERK1) activation	0.028571429	0.00179 5472	0.0052581 68	PTPN11/CDK1	2
R-HSA-1250342	PI3K events in ERBB4 signaling	0.028571429	0.00179 5472	0.0052581 68	PIK3R1/PIK3CA	2
R-HSA-5655302	Signaling by FGFR1 in disease	0.042857143	0.00186 0142	0.0054260 27	PIK3R1/PIK3CA/GRB2	3
R-HSA-76009	Platelet Aggregation (Plug Formation)	0.042857143	0.00200 5873	0.0057932 71	SHC1/PTK2/GRB2	3
R-HSA-8853884	Transcriptional Regulation by VENTX	0.042857143	0.00200 5873	0.0057932 71	CDKN2A/CTNNB1/CEBPB	3
R-HSA-69202	Cyclin E associated events during G1/S transition	0.057142857	0.00200 959	0.0057932 71	CDKN1A/MYC/CCNA2/E2F1	4
R-HSA-73886	Chromosome Maintenance	0.071428571	0.00201 7779	0.0057942 44	BLM/WRN/TERT/CCNA2/P CNA	5
R-HSA-381340	Transcriptional regulation of white adipocyte differentiation	0.057142857	0.00209 9882	0.0060066 38	HDAC3/CEBPA/CEBPB/NCOR2	4
R-HSA-5693616	Presynaptic phase of homologous DNA pairing and strand exchange	0.042857143	0.00215 8526	0.0060613 9	BLM/WRN/ATM	3
R-HSA-9013420	RHO GTPase cycle	0.042857143	0.00215 8526	0.0060613 9	PIK3R1/CDC42/GRB2	3
R-HSA-2586552	Signaling by Leptin	0.028571429	0.00218 5304	0.0060613 9	PTPN11/IRS1	2
R-HSA-4755510	SUMOylation of immune response proteins	0.028571429	0.00218 5304	0.0060613 9	NFKB2/NFKBIA	2
R-HSA-8851805	MET activates RAS signaling	0.028571429	0.00218 5304	0.0060613 9	SHC1/GRB2	2
R-HSA-9028731	Activated NTRK2 signals through FRS2 and FRS3	0.028571429	0.00218 5304	0.0060613 9	PTPN11/GRB2	2
R-HSA-9614399	Regulation of localization of FOXO transcription factors	0.028571429	0.00218 5304	0.0060613 9	FOXO1/FOXO3	2
R-HSA-9634285	Constitutive Signaling by Overexpressed ERBB2	0.028571429	0.00218 5304	0.0060613 9	SHC1/GRB2	2
R-HSA-69656	Cyclin A:Cdk2-associated events at S phase entry	0.057142857	0.00219 2942	0.0060613 9	CDKN1A/MYC/CCNA2/E2F1	4
R-HSA-5696400	Dual Incision in GG-NER	0.042857143	0.00231 8215	0.0063364 54	ERCC1/PCNA/XPA	3
R-HSA-9675136	Diseases of DNA Double-Strand Break Repair	0.042857143	0.00231 8215	0.0063364 54	BLM/WRN/ATM	3
R-HSA-9701190	Defective homologous recombination repair (HRR) due to BRCA2 loss of function	0.042857143	0.00231 8215	0.0063364 54	BLM/WRN/ATM	3

SUPPLEMENTARY DATA

R-HSA-73887	Death Receptor Signalling	0.071428571	0.00250 0312	0.0068089 69	NFKBIA/IKBKB/HDAC3/PS EN1/HDAC2	5
R-HSA-389359	CD28 dependent Vav1 pathway	0.028571429	0.00261 1421	0.0070594 45	CDC42/GRB2	2
R-HSA-9027276	Erythropoietin activates Phosphoinositide-3-kinase (PI3K)	0.028571429	0.00261 1421	0.0070594 45	PIK3R1/PIK3CA	2
R-HSA-5655253	Signaling by FGFR2 in disease	0.042857143	0.00265 9137	0.0071361 57	PIK3R1/PIK3CA/GRB2	3
R-HSA-5693579	Homologous DNA Pairing and Strand Exchange	0.042857143	0.00265 9137	0.0071361 57	BLM/WRN/ATM	3
R-HSA-416476	G alpha (q) signalling events	0.085714286	0.00267 3542	0.0071488 2	CREB1/APP/AGTR1/PIK3R1 /PIK3CA/GRB2	6
R-HSA-1592230	Mitochondrial biogenesis	0.057142857	0.00304 222	0.0080761 09	CREB1/HDAC3/MAPK14/SI RT3	4
R-HSA-170834	Signaling by TGF-beta Receptor Complex	0.057142857	0.00304 222	0.0080761 09	MYC/SP1/CDKN2B/NCOR2	4
R-HSA-179812	GRB2 events in EGFR signaling	0.028571429	0.00307 3351	0.0081004 75	EGF/GRB2	2
R-HSA-209560	NF-kB is activated and signals survival	0.028571429	0.00307 3351	0.0081004 75	NFKBIA/IKBKB	2
R-HSA-9024446	NR1H2 and NR1H3-mediated signaling	0.042857143	0.00322 5944	0.0084724 09	APOE/HDAC3/NCOR2	3
R-HSA-202424	Downstream TCR signaling	0.057142857	0.00354 1096	0.0091816 11	NFKBIA/IKBKB/PIK3R1/PI K3CA	4
R-HSA-1250347	SHC1 events in ERBB4 signaling	0.028571429	0.00357 0627	0.0091816 11	SHC1/GRB2	2
R-HSA-198323	AKT phosphorylates targets in the cytosol	0.028571429	0.00357 0627	0.0091816 11	CDKN1A/MDM2	2
R-HSA-418885	DCC mediated attractive signaling	0.028571429	0.00357 0627	0.0091816 11	CDC42/PTK2	2
R-HSA-8983432	Interleukin-15 signaling	0.028571429	0.00357 0627	0.0091816 11	SHC1/GRB2	2
R-HSA-9027284	Erythropoietin activates RAS	0.028571429	0.00357 0627	0.0091816 11	SHC1/GRB2	2
R-HSA-9679191	Potential therapeutics for SARS	0.057142857	0.00367 3995	0.0094146 12	VEGFA/NFE2L2/HDAC2/GR B2	4
R-HSA-69242	S Phase	0.071428571	0.00401 5164	0.0102532 57	CDKN1A/MYC/CCNA2/PCN A/E2F1	5
R-HSA-354194	GRB2:SOS provides linkage to MAPK signaling for Integrins	0.028571429	0.00410 2784	0.0104408 78	PTK2/GRB2	2
R-HSA-9675135	Diseases of DNA repair	0.042857143	0.00432 4856	0.0109650 89	BLM/WRN/ATM	3
R-HSA-69481	G2/M Checkpoints	0.071428571	0.00433 849	0.0109650 89	BLM/WRN/CDK1/TP53BP1/ ATM	5
R-HSA-2980766	Nuclear Envelope Breakdown	0.042857143	0.00456 8575	0.0115071 95	CDK1/LMNA/LMNB1	3
R-HSA-1295596	Spry regulation of FGF signaling	0.028571429	0.00466 9365	0.0115637 29	PTPN11/GRB2	2
R-HSA-193639	p75NTR signals via NF-kB	0.028571429	0.00466 9365	0.0115637 29	NFKBIA/IKBKB	2

SUPPLEMENTARY DATA

R-HSA-1963640	GRB2 events in ERBB2 signaling	0.028571429	0.00466 9365	0.0115637 29	EGF/GRB2	2
R-HSA-844456	The NLRP3 inflammasome	0.028571429	0.00466 9365	0.0115637 29	NFKB2/APP	2
R-HSA-9614657	FOXO-mediated transcription of cell death genes	0.028571429	0.00466 9365	0.0115637 29	FOXO1/FOXO3	2
R-HSA-8856825	Cargo recognition for clathrin-mediated endocytosis	0.057142857	0.00470 0389	0.0116016 28	EGF/AGTR1/IL7R/GRB2	4
R-HSA-9679506	SARS-CoV Infections	0.114285714	0.00479 7154	0.0118009 98	PTPN11/VEGFA/NFKBIA/IKBKB/NFE2L2/SP1/HDAC2/GRB2	8
R-HSA-174437	Removal of the Flap Intermediate from the C-strand	0.028571429	0.00526 9914	0.0127934 09	WRN/PCNA	2
R-HSA-432142	Platelet sensitization by LDL	0.028571429	0.00526 9914	0.0127934 09	PTPN11/MAPK14	2
R-HSA-9659787	Aberrant regulation of mitotic G1/S transition in cancer due to RB1 defects	0.028571429	0.00526 9914	0.0127934 09	CDKN1A/E2F1	2
R-HSA-9661069	Defective binding of RB1 mutants to E2F1,(E2F2, E2F3)	0.028571429	0.00526 9914	0.0127934 09	CDKN1A/E2F1	2
R-HSA-109606	Intrinsic Pathway for Apoptosis	0.042857143	0.00534 907	0.0129429 96	CDKN2A/E2F1/BAX	3
R-HSA-2151201	Transcriptional activation of mitochondrial biogenesis	0.042857143	0.00562 5931	0.0135684 22	CREB1/HDAC3/SIRT3	3
R-HSA-5654704	SHC-mediated cascade:FGFR3	0.028571429	0.00590 398	0.0140726 1	SHC1/GRB2	2
R-HSA-881907	Gastrin-CREB signalling pathway via PKC and MAPK	0.028571429	0.00590 398	0.0140726 1	CREB1/GRB2	2
R-HSA-983705	Signaling by the B Cell Receptor (BCR)	0.057142857	0.00590 4433	0.0140726 1	NFKBIA/IKBKB/PIK3R1/GRB2	4
R-HSA-69541	Stabilization of p53	0.042857143	0.00591 1259	0.0140726 1	CDKN2A/MDM2/ATM	3
R-HSA-6804760	Regulation of TP53 Activity through Methylation	0.028571429	0.00657 1119	0.0155932 01	MDM2/ATM	2
R-HSA-1989781	PPARA activates gene expression	0.057142857	0.00667 7131	0.0157939 82	CLOCK/HDAC3/SP1/NCOR2	4
R-HSA-1500620	Meiosis	0.057142857	0.00688 0284	0.0162225 22	BLM/LMNA/LMNB1/ATM	4
R-HSA-198725	Nuclear Events (kinase and transcription factor activation)	0.042857143	0.00713 8562	0.0167778 95	CREB1/MAPK14/EGR1	3
R-HSA-111471	Apoptotic factor-mediated response	0.028571429	0.00727 0887	0.0168210 49	CDKN2A/BAX	2
R-HSA-5654706	FRS-mediated FGFR3 signaling	0.028571429	0.00727 0887	0.0168210 49	PTPN11/GRB2	2

SUPPLEMENTARY DATA

R-HSA-5654719	SHC-mediated cascade:FGFR4	0.028571429	0.00727 0887	0.0168210 49	SHC1/GRB2	2
R-HSA-6803204	TP53 Regulates Transcription of Genes Involved in Cytochrome C Release	0.028571429	0.00727 0887	0.0168210 49	ATM/BAX	2
R-HSA-8876384	Listeria monocytogenes entry into host cells	0.028571429	0.00727 0887	0.0168210 49	CTNNB1/GRB2	2
R-HSA-202403	TCR signaling	0.057142857	0.00729 8804	0.0168328 68	NFKBIA/IKBKB/PIK3R1/PIK3CA	4
R-HSA-1226099	Signaling by FGFR in disease	0.042857143	0.00780 467	0.0178877 22	PIK3R1/PIK3CA/GRB2	3
R-HSA-375165	NCAM signaling for neurite out-growth	0.042857143	0.00780 467	0.0178877 22	CREB1/PTK2/GRB2	3
R-HSA-9006936	Signaling by TGFB family members	0.057142857	0.00795 7627	0.0181818 22	MYC/SP1/CDKN2B/NCOR2	4
R-HSA-622312	Inflammasomes	0.028571429	0.00800 2847	0.0182287 08	NFKB2/APP	2
R-HSA-6782135	Dual incision in TC-NER	0.042857143	0.00850 6351	0.0193159 6	ERCC1/PCNA/XPA	3
R-HSA-453274	Mitotic G2-G2/M phases	0.071428571	0.00866 3321	0.0196120 57	CDKN1A/CDK1/CCNA2/E2F1/FOXM1	5
R-HSA-113510	E2F mediated regulation of DNA replication	0.028571429	0.00876 6566	0.0196648 2	CDK1/E2F1	2
R-HSA-389357	CD28 dependent PI3K/Akt signaling	0.028571429	0.00876 6566	0.0196648 2	PIK3R1/PIK3CA	2
R-HSA-5654712	FRS-mediated FGFR4 signaling	0.028571429	0.00876 6566	0.0196648 2	PTPN11/GRB2	2
R-HSA-112409	RAF-independent MAPK1/3 activation	0.028571429	0.00956 1614	0.0211906 04	PTPN11/CDK1	2
R-HSA-171319	Telomere Extension By Telomerase	0.028571429	0.00956 1614	0.0211906 04	TERT/CCNA2	2
R-HSA-373753	Nephrin family interactions	0.028571429	0.00956 1614	0.0211906 04	PIK3R1/PIK3CA	2
R-HSA-5654699	SHC-mediated cascade:FGFR2	0.028571429	0.00956 1614	0.0211906 04	SHC1/GRB2	2
R-HSA-400253	Circadian Clock	0.042857143	0.00962 6457	0.0212461 75	CREB1/CLOCK/HDAC3	3
R-HSA-114608	Platelet degranulation	0.057142857	0.00964 4266	0.0212461 75	SOD1/VEGFA/EGF/APP	4
R-HSA-5668599	RHO GTPases Activate NADPH Oxidases	0.028571429	0.01038 7565	0.0227478 44	MAPK14/PIN1	2
R-HSA-8940973	RUNX2 regulates osteoblast differentiation	0.028571429	0.01038 7565	0.0227478 44	HDAC3/ABL1	2
R-HSA-76005	Response to elevated platelet cytosolic Ca ²⁺	0.057142857	0.01098 1666	0.0239777 2	SOD1/VEGFA/EGF/APP	4
R-HSA-2029485	Role of phospholipids in phagocytosis	0.028571429	0.01124 3999	0.0243345 21	PIK3R1/PIK3CA	2
R-HSA-5654700	FRS-mediated FGFR2 signaling	0.028571429	0.01124 3999	0.0243345 21	PTPN11/GRB2	2

SUPPLEMENTARY DATA

R-HSA-9013507	NOTCH3 Activation and Transmission of Signal to the Nucleus	0.028571429	0.01124 3999	0.0243345 21	EGF/PSEN1	2
R-HSA-174184	Cdc20:Phospho-APC/C mediated degradation of Cyclin A	0.042857143	0.01167 649	0.0251966 36	CDK1/CCNA2/BUB1B	3
R-HSA-179419	APC:Cdc20 mediated degradation of cell cycle proteins prior to satisfaction of the cell cycle checkpoint	0.042857143	0.01211 4326	0.0258737 22	CDK1/CCNA2/BUB1B	3
R-HSA-2995410	Nuclear Envelope (NE) Reassembly	0.042857143	0.01211 4326	0.0258737 22	CDK1/LMNA/LMNB1	3
R-HSA-9660826	Purinergic signaling in leishmaniasis infection	0.028571429	0.01213 0498	0.0258737 22	NFKB2/APP	2
R-HSA-9664424	Cell recruitment (pro-inflammatory response)	0.028571429	0.01213 0498	0.0258737 22	NFKB2/APP	2
R-HSA-6807070	PTEN Regulation	0.057142857	0.01243 3692	0.0264439 9	JUN/HDAC3/HDAC2/EGR1	4
R-HSA-176409	APC/C:Cdc20 mediated degradation of mitotic proteins	0.042857143	0.01301 8098	0.0274314 16	CDK1/CCNA2/BUB1B	3
R-HSA-3108214	SUMOylation of DNA damage response and repair proteins	0.042857143	0.01301 8098	0.0274314 16	CDKN2A/BLM/WRN	3
R-HSA-5693565	Recruitment and ATM-mediated phosphorylation of repair and signaling proteins at DNA double strand breaks	0.042857143	0.01301 8098	0.0274314 16	TP53BP1/ABL1/ATM	3
R-HSA-5620971	Pyroptosis	0.028571429	0.01304 6649	0.0274314 16	HMGB1/BAX	2
R-HSA-1474165	Reproduction	0.057142857	0.01336 1322	0.0280132 25	BLM/LMNA/LMNB1/ATM	4
R-HSA-176814	Activation of APC/C and APC/C:Cdc20 mediated degradation of mitotic proteins	0.042857143	0.01348 4093	0.0281109 06	CDK1/CCNA2/BUB1B	3
R-HSA-5693606	DNA Double Strand Break Response	0.042857143	0.01348 4093	0.0281109 06	TP53BP1/ABL1/ATM	3
R-HSA-6781827	Transcription-Coupled Nucleotide Excision Repair (TC-NER)	0.042857143	0.01395 9531	0.0290200 96	ERCC1/PCNA/XPA	3
R-HSA-8856828	Clathrin-mediated endocytosis	0.057142857	0.01433 2094	0.0297109 13	EGF/AGTR1/IL7R/GRB2	4
R-HSA-9759194	Nuclear events mediated by NFE2L2	0.042857143	0.01444 4438	0.0298599 3	CDKN2A/MYC/NFE2L2	3
R-HSA-5654732	Negative regulation of FGFR3 signaling	0.028571429	0.01496 6273	0.0308522 61	PTPN11/GRB2	2

SUPPLEMENTARY DATA

R-HSA-176408	Regulation of APC/C activators between G1/S and early anaphase	0.042857143	0.01544 2747	0.0317458 14	CDK1/CCNA2/BUB1B	3
R-HSA-6804758	Regulation of TP53 Activity through Acetylation	0.028571429	0.01596 8939	0.0327363 24	PIN1/HDAC2	2
R-HSA-5654733	Negative regulation of FGFR4 signaling	0.028571429	0.01699 9642	0.0345858 85	PTPN11/GRB2	2
R-HSA-8941326	RUNX2 regulates bone development	0.028571429	0.01699 9642	0.0345858 85	HDAC3/ABL1	2
R-HSA-5696399	Global Genome Nucleotide Excision Repair (GG-NER)	0.042857143	0.01701 1757	0.0345858 85	ERCC1/PCNA/XPA	3
R-HSA-5626467	RHO GTPases activate IQGAPs	0.028571429	0.01805 799	0.0365117 72	CTNNB1/CDC42	2
R-HSA-983695	Antigen activates B Cell Receptor (BCR) leading to generation of second messengers	0.028571429	0.01805 799	0.0365117 72	PIK3R1/GRB2	2
R-HSA-1980145	Signaling by NOTCH2	0.028571429	0.01914 3592	0.0383720 17	CREB1/PSEN1	2
R-HSA-2871809	FCERI mediated Ca ²⁺ mobilization	0.028571429	0.01914 3592	0.0383720 17	SHC1/GRB2	2
R-HSA-174143	APC/C-mediated degradation of cell cycle proteins	0.042857143	0.01923 8003	0.0383720 17	CDK1/CCNA2/BUB1B	3
R-HSA-453276	Regulation of mitotic cell cycle	0.042857143	0.01923 8003	0.0383720 17	CDK1/CCNA2/BUB1B	3
R-HSA-9013404	RAC2 GTPase cycle	0.042857143	0.01923 8003	0.0383720 17	PIK3R1/CDC42/PIK3CA	3
R-HSA-5654727	Negative regulation of FGFR2 signaling	0.028571429	0.02025 6061	0.0402937 29	PTPN11/GRB2	2
R-HSA-201722	Formation of the beta-catenin:TCF transactivating complex	0.042857143	0.02040 8871	0.0404885 66	MYC/TERT/CTNNB1	3
R-HSA-1912408	Pre-NOTCH Transcription and Translation	0.042857143	0.02161 8319	0.0426586 08	JUN/SIRT6/E2F1	3
R-HSA-2682334	EPH-Ephrin signaling	0.042857143	0.02161 8319	0.0426586 08	PSEN1/CDC42/PTK2	3
R-HSA-381119	Unfolded Protein Response (UPR)	0.042857143	0.02223 7522	0.0437634 43	LMNA/SHC1/CEBPB	3
R-HSA-168638	NOD1/2 Signaling Pathway	0.028571429	0.02256 0077	0.0441626 97	IKBKB/MAPK14	2
R-HSA-9687139	Aberrant regulation of mitotic cell cycle due to RB1 defects	0.028571429	0.02256 0077	0.0441626 97	CDKN1A/E2F1	2
R-HSA-3214815	HDACs deacetylate histones	0.042857143	0.02286 6382	0.0446438 88	HDAC3/HDAC2/NCOR2	3
R-HSA-983231	Factors involved in megakaryocyte development and platelet production	0.057142857	0.02327 0663	0.0453133 24	CDC42/ABL1/HDAC2/SIN3 A	4

SUPPLEMENTARY DATA

R-HSA-3299685	Detoxification of Reactive Oxygen Species	0.028571429	0.023750869	0.04600562	SOD1/CAT	2
R-HSA-9013424	RHOV GTPase cycle	0.028571429	0.023750869	0.04600562	PIK3R1/CDC42	2
R-HSA-9675126	Diseases of mitotic cell cycle	0.028571429	0.02496702	0.048234714	CDKN1A/E2F1	2

Supplementary Table 6. Significantly enriched reactome pathways for 84 aging-specific novel targets

ID	Description	GeneRatio	pvalue	p.adjust	geneID	Count
R-HSA-9009391	Extra-nuclear estrogen signaling	0.108433735	6.24E-09	4.46E-06	AKT2/NOS3/CCND1/CAV1/MAPK1/AKT3/MMP7/ESR2/XPO1	9
R-HSA-199418	Negative regulation of the PI3K/AKT network	0.120481928	1.33E-08	4.74E-06	CD19/AKT2/FYN/CD28/MAPK1/AKT3/MET/PIK3CD/ESR2/KIT	10
R-HSA-8878166	Transcriptional regulation by RUNX2	0.120481928	2.37E-08	5.66E-06	HDAC4/AKT2/CCND1/MAPK1/CDK4/RUNX2/SMAD4/AKT3/COL1A1/MMP13	10
R-HSA-2219528	PI3K/AKT Signaling in Cancer	0.108433735	8.99E-08	1.47E-05	CD19/AKT2/FYN/CD28/AKT3/MET/PIK3CD/ESR2/KIT	9
R-HSA-8939211	ESR-mediated signaling	0.144578313	1.11E-07	1.47E-05	AKT2/NOS3/CCND1/CAV1/MAPK1/AKT3/MMP7/MYB/ESR2/XPO1/FOSB/H2BC21	12
R-HSA-6785807	Interleukin-4 and Interleukin-13 signaling	0.108433735	1.25E-07	1.47E-05	CCND1/CCL2/VIM/SOX2/IL4/SOCS3/ICAM1/IL18/ITGAM	9
R-HSA-5663202	Diseases of signal transduction by growth factor receptors and second messengers	0.192771084	1.44E-07	1.47E-05	CD19/HDAC4/AKT2/FYN/CD28/SMAD3/TGFBR1/MAPK1/CTBP1/SMAD4/AKT3/BRAF/MET/PIK3CD/ESR2/KIT	16
R-HSA-9006931	Signaling by Nuclear Receptors	0.156626506	3.65E-07	3.26E-05	AKT2/NOS3/CCND1/CAV1/RXR/MAPK1/AKT3/MMP7/MYB/ESR2/XPO1/FOSB/H2BC21	13
R-HSA-9634638	Estrogen-dependent nuclear events downstream of ESR-membrane signaling	0.060240964	8.91E-07	7.08E-05	AKT2/CCND1/MAPK1/AKT3/XPO1	5
R-HSA-6811558	PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling	0.096385542	1.40E-06	9.98E-05	CD19/FYN/CD28/MAPK1/MET/PIK3CD/ESR2/KIT	8
R-HSA-2219530	Constitutive Signaling by Aberrant PI3K in Cancer	0.084337349	2.06E-06	0.000133866	CD19/FYN/CD28/MET/PIK3CD/ESR2/KIT	7
R-HSA-449147	Signaling by Interleukins	0.180722892	2.49E-06	0.000148445	IL3/FYN/CCND1/SMAD3/CCCL2/VIM/SOX2/IL4/MAPK1/SOCS3/ICAM1/IL18/PIK3CD/IKBKG/ITGAM	15
R-HSA-8941326	RUNX2 regulates bone development	0.060240964	3.42E-06	0.000187912	HDAC4/MAPK1/RUNX2/SMAD4/COL1A1	5
R-HSA-216083	Integrin cell surface interactions	0.084337349	3.69E-06	0.000188215	CD44/PECAM1/ICAM1/COL1A1/ITGAM/SPP1/THBS1	7
R-HSA-1257604	PIP3 activates AKT signaling	0.13253012	5.43E-06	0.000258791	CD19/AKT2/FYN/CD28/MAPK1/AKT3/MET/REST/PIK3CD/ESR2/KIT	11

SUPPLEMENTARY DATA

R-HSA-1474244	Extracellular matrix organization	0.1325 3012	1.69E-05	0.000756256	CD44/PECAM1/HTRA1/ICAM1/LAMB2/MMP7/COL1A1/ITGAM/MMP13/SPP1/THBS1	11
R-HSA-389357	CD28 dependent PI3K/Akt signaling	0.0481 92771	2.12E-05	0.00085873	AKT2/FYN/CD28/AKT3	4
R-HSA-9006925	Intracellular signaling by second messengers	0.1325 3012	2.16E-05	0.00085873	CD19/AKT2/FYN/CD28/MAPK1/AKT3/MET/REST/PIK3CD/ESR2/KIT	11
R-HSA-452723	Transcriptional regulation of pluripotent stem cells	0.0481 92771	2.55E-05	0.000959968	SOX2/SMAD4/EPAS1/NR5A1	4
R-HSA-8848021	Signaling by PTK6	0.0602 40964	5.54E-05	0.001885798	CCND1/CDK4/SOCS3/EPAS1/LRRK2	5
R-HSA-9006927	Signaling by Non-Receptor Tyrosine Kinases	0.0602 40964	5.54E-05	0.001885798	CCND1/CDK4/SOCS3/EPAS1/LRRK2	5
R-HSA-5218920	VEGFR2 mediated vascular permeability	0.0481 92771	6.61E-05	0.002147174	AKT2/NOS3/CAV1/AKT3	4
R-HSA-166520	Signaling by NTRKs	0.0843 37349	7.25E-05	0.002253424	FYN/ADORA2A/MAPK1/GRI N2B/BRAF/REST/FOSB	7
R-HSA-4090294	SUMOylation of intracellular receptors	0.0481 92771	7.58E-05	0.002257836	HDAC4/RXRA/NR3C2/NR5A1	4
R-HSA-202733	Cell surface interactions at the vascular wall	0.0843 37349	8.34E-05	0.002384896	FYN/CD44/CAV1/PECAM1/COL1A1/APOB/ITGAM	7
R-HSA-9755779	SARS-CoV-2 targets host intracellular signalling and regulatory pathways	0.0361 44578	9.11E-05	0.002505279	AKT2/CAV1/AKT3	3
R-HSA-389356	CD28 co-stimulation	0.0481 92771	0.0001112	0.002944735	AKT2/FYN/CD28/AKT3	4
R-HSA-9634815	Transcriptional Regulation by NPAS4	0.0481 92771	0.0001252 94	0.003199465	ARNT/MAPK1/REST/XPO1	4
R-HSA-9614085	FOXO-mediated transcription	0.0602 40964	0.0001354 28	0.003339007	AKT2/SMAD3/CAV1/SMAD4/AKT3	5
R-HSA-1502540	Signaling by Activin	0.0361 44578	0.0001853 05	0.004273969	SMAD3/MAPK1/SMAD4	3
R-HSA-9735871	SARS-CoV-1 targets host intracellular signalling and regulatory pathways	0.0361 44578	0.0001853 05	0.004273969	SMAD3/CAV1/SMAD4	3
R-HSA-9617828	FOXO-mediated transcription of cell cycle genes	0.0361 44578	0.0002738 87	0.005934219	SMAD3/CAV1/SMAD4	3
R-HSA-9754189	Germ layer formation at gastrulation	0.0361 44578	0.0002738 87	0.005934219	SMAD3/SOX2/SMAD4	3
R-HSA-3769402	Deactivation of the beta-catenin transactivating complex	0.0481 92771	0.0002886 3	0.006069713	AKT2/SOX2/CTBP1/XPO1	4
R-HSA-9758941	Gastrulation	0.0361 44578	0.0003859 9	0.007885228	SMAD3/SOX2/SMAD4	3
R-HSA-2173789	TGF-beta receptor signaling activates SMADs	0.0481 92771	0.0004111 17	0.008165235	SMAD3/TGFBR1/SMAD4/XPO1	4
R-HSA-9707616	Heme signaling	0.0481 92771	0.0004467 54	0.008633216	RXRA/XPO1/APOB/CRTC1	4

SUPPLEMENTARY DATA

R-HSA-3108232	SUMO E3 ligases SUMOylate target proteins	0.0843 37349	0.0004645 79	0.008741418	HDAC4/DNMT3A/RXRA/NR 3C2/CTBP1/NR5A1/IKBKG	7
R-HSA-1181150	Signaling by NODAL	0.0361 44578	0.0005239 59	0.00936576	SMAD3/MAPK1/SMAD4	3
R-HSA-389513	CTLA4 inhibitory signaling	0.0361 44578	0.0005239 59	0.00936576	AKT2/FYN/AKT3	3
R-HSA-2990846	SUMOylation	0.0843 37349	0.0005647 6	0.009848869	HDAC4/DNMT3A/RXRA/NR 3C2/CTBP1/NR5A1/IKBKG	7
R-HSA-9768919	NPAS4 regulates expression of target genes	0.0361 44578	0.0006033 42	0.01027118	ARNT/MAPK1/XPO1	3
R-HSA-9711123	Cellular response to chemical stress	0.0843 37349	0.0006406 08	0.010651978	AKT2/CYCS/RXRA/ALB/AK T3/IDH1/ATF4	7
R-HSA-383280	Nuclear Receptor transcription pathway	0.0481 92771	0.0006586 63	0.010703267	RXRA/NR3C2/ESR2/NR5A1	4
R-HSA-1474228	Degradation of the extracellular matrix	0.0722 89157	0.0007026 98	0.011165085	CD44/HTRA1/MMP7/COL1A 1/MMP13/SPP1	6
R-HSA-170834	Signaling by TGF-beta Receptor Complex	0.0602 40964	0.0007206 99	0.011202165	SMAD3/TGFBR1/MAPK1/SM AD4/XPO1	5
R-HSA-8940973	RUNX2 regulates osteoblast differentiation	0.0361 44578	0.0007842 43	0.011930507	MAPK1/RUNX2/COL1A1	3
R-HSA-109606	Intrinsic Pathway for Apoptosis	0.0481 92771	0.0008154 37	0.012146612	AKT2/CYCS/MAPK1/AKT3	4
R-HSA-8878159	Transcriptional regulation by RUNX3	0.0602 40964	0.0008325 74	0.012148777	HDAC4/CCND1/SMAD3/SM AD4/SPP1	5
R-HSA-76002	Platelet activation, signaling and aggregation	0.0963 85542	0.0008945 07	0.012791447	FYN/MAPK1/PECAM1/ALB/ COL1A1/HSPA5/SELENOP/T HBS1	8
R-HSA-4420097	VEGFA-VEGFR2 Pathway	0.0602 40964	0.0009569 29	0.013415774	AKT2/FYN/NOS3/CAV1/AKT 3	5
R-HSA-2173788	Downregulation of TGF- beta receptor signaling	0.0361 44578	0.0009963 55	0.013699875	SMAD3/TGFBR1/XPO1	3
R-HSA-211976	Endogenous sterols	0.0361 44578	0.0011147 25	0.015038271	RXRA/ARNT/AHR	3
R-HSA-194138	Signaling by VEGF	0.0602 40964	0.0014134 28	0.018374569	AKT2/FYN/NOS3/CAV1/AKT 3	5
R-HSA-8957275	Post-translational protein phosphorylation	0.0602 40964	0.0014134 28	0.018374569	C3/ALB/LAMB2/APOB/SPP1	5
R-HSA-2173795	Downregulation of SMAD2/3:SMAD4 transcriptional activity	0.0361 44578	0.0015218 66	0.019090071	SMAD3/MAPK1/SMAD4	3
R-HSA-8874081	MET activates PTK2 signaling	0.0361 44578	0.0015218 66	0.019090071	LAMB2/MET/COL1A1	3
R-HSA-381042	PERK regulates gene expression	0.0361 44578	0.0018388 29	0.022243312	CCL2/HSPA5/ATF4	3
R-HSA-983695	Antigen activates B Cell Receptor (BCR) leading to generation of second messengers	0.0361 44578	0.0018388 29	0.022243312	CD19/FYN/PIK3CD	3
R-HSA-187037	Signaling by NTRK1 (TRKA)	0.0602 40964	0.0018665 72	0.022243312	ADORA2A/MAPK1/BRAF/R EST/FOSB	5
R-HSA-388841	Costimulation by the CD28 family	0.0481 92771	0.0019057 61	0.022311015	AKT2/FYN/CD28/AKT3	4
R-HSA-201681	TCF dependent signaling in response to WNT	0.0843 37349	0.0019346 61	0.022311015	AKT2/SOX2/CAV1/CTBP1/H 3-4/XPO1/H2BC21	7

SUPPLEMENTARY DATA

R-HSA-8878171	Transcriptional regulation by RUNX1	0.0843 37349	0.0022367 85	0.025385729	IL3/CCND1/SOCS3/RUNX2/MYB/H2BC21/THBS1	7
R-HSA-9006936	Signaling by TGFB family members	0.0602 40964	0.0024181 25	0.027014993	SMAD3/TGFBR1/MAPK1/SMAD4/XPO1	5
R-HSA-381183	ATF6 (ATF6-alpha) activates chaperone genes	0.0240 96386	0.0025138 42	0.027652258	HSPA5/ATF4	2
R-HSA-2173796	SMAD2/SMAD3:SMAD4 heterotrimer regulates transcription	0.0361 44578	0.0025893 21	0.028050981	SMAD3/MAPK1/SMAD4	3
R-HSA-381426	Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)	0.0602 40964	0.0026875 32	0.028680376	C3/ALB/LAMB2/APOB/SPP1	5
R-HSA-9607240	FLT3 Signaling	0.0361 44578	0.0030258 19	0.030165307	AKT2/FYN/AKT3	3
R-HSA-111458	Formation of apoptosome	0.0240 96386	0.0030572 05	0.030165307	CYCS/MAPK1	2
R-HSA-1234158	Regulation of gene expression by Hypoxia-inducible Factor	0.0240 96386	0.0030572 05	0.030165307	ARNT/EPAS1	2
R-HSA-9614399	Regulation of localization of FOXO transcription factors	0.0240 96386	0.0030572 05	0.030165307	AKT2/AKT3	2
R-HSA-9627069	Regulation of the apoptosome activity	0.0240 96386	0.0030572 05	0.030165307	CYCS/MAPK1	2
R-HSA-114608	Platelet degranulation	0.0602 40964	0.0030798 15	0.030165307	PECAM1/ALB/HSPA5/SELENO/THBS1	5
R-HSA-5683057	MAPK family signaling cascades	0.0963 85542	0.0033250 86	0.032127521	IL3/FYN/MAPK1/GRIN2B/BRAF/MET/XPO1/KIT	8
R-HSA-76005	Response to elevated platelet cytosolic Ca ²⁺	0.0602 40964	0.0036264 32	0.033038665	PECAM1/ALB/HSPA5/SELENO/THBS1	5
R-HSA-170968	Frs2-mediated activation	0.0240 96386	0.0036504 26	0.033038665	MAPK1/BRAF	2
R-HSA-210990	PECAM1 interactions	0.0240 96386	0.0036504 26	0.033038665	FYN/PECAM1	2
R-HSA-381033	ATF6 (ATF6-alpha) activates chaperones	0.0240 96386	0.0036504 26	0.033038665	HSPA5/ATF4	2
R-HSA-389359	CD28 dependent Vav1 pathway	0.0240 96386	0.0036504 26	0.033038665	FYN/CD28	2
R-HSA-69202	Cyclin E associated events during G1/S transition	0.0481 92771	0.0037358 78	0.033198484	AKT2/CCND1/CDK4/AKT3	4
R-HSA-8875878	MET promotes cell motility	0.0361 44578	0.0037609 47	0.033198484	LAMB2/MET/COL1A1	3
R-HSA-2173782	Binding and Uptake of Ligands by Scavenger Receptors	0.0361 44578	0.0040280 49	0.034635948	ALB/COL1A1/APOB	3
R-HSA-9679506	SARS-CoV Infections	0.1084 33735	0.0040599 34	0.034635948	AKT2/SMAD3/CAV1/STING1/SMAD4/AKT3/GJA1/REST/IKKKG	9
R-HSA-69656	Cyclin A:Cdk2-associated events at S phase entry	0.0481 92771	0.0040691 18	0.034635948	AKT2/CCND1/CDK4/AKT3	4

SUPPLEMENTARY DATA

R-HSA-111461	Cytochrome c-mediated apoptotic response	0.0240 96386	0.0042927 26	0.035279298	CYCS/MAPK1	2
R-HSA-1358803	Downregulation of ERBB2:ERBB3 signaling	0.0240 96386	0.0042927 26	0.035279298	AKT2/AKT3	2
R-HSA-203615	eNOS activation	0.0240 96386	0.0042927 26	0.035279298	NOS3/CAV1	2
R-HSA-9705683	SARS-CoV-2-host interactions	0.0722 89157	0.0043968 78	0.035724635	AKT2/CAV1/STING1/AKT3/GJA1/IKBKG	6
R-HSA-9616222	Transcriptional regulation of granulopoiesis	0.0481 92771	0.0047948 55	0.03831274	RXRA/CDK4/MYB/H2BC21	4
R-HSA-162658	Golgi Cisternae Pericentriolar Stack Reorganization	0.0240 96386	0.0049833 35	0.03831274	MAPK1/PLK1	2
R-HSA-169893	Prolonged ERK activation events	0.0240 96386	0.0049833 35	0.03831274	MAPK1/BRAF	2
R-HSA-198323	AKT phosphorylates targets in the cytosol	0.0240 96386	0.0049833 35	0.03831274	AKT2/AKT3	2
R-HSA-6804759	Regulation of TP53 Activity through Association with Co-factors	0.0240 96386	0.0049833 35	0.03831274	AKT2/AKT3	2
R-HSA-73884	Base Excision Repair	0.0481 92771	0.0051883 86	0.039055289	OGG1/PARP2/H3-4/H2BC21	4
R-HSA-5357801	Programmed Cell Death	0.0722 89157	0.0051891 64	0.039055289	AKT2/CYCS/VIM/MAPK1/AKT3/IL18	6
R-HSA-5673001	RAF/MAP kinase cascade	0.0843 37349	0.0054951 69	0.040801828	IL3/FYN/MAPK1/GRIN2B/BRAF/MET/KIT	7
R-HSA-6783783	Interleukin-10 signaling	0.0361 44578	0.0055353 53	0.040801828	CCL2/ICAM1/IL18	3
R-HSA-111447	Activation of BAD and translocation to mitochondria	0.0240 96386	0.0057214 94	0.041321901	AKT2/AKT3	2
R-HSA-75892	Platelet Adhesion to exposed collagen	0.0240 96386	0.0057214 94	0.041321901	FYN/COL1A1	2
R-HSA-512988	Interleukin-3, Interleukin-5 and GM-CSF signaling	0.0361 44578	0.0058720 74	0.041985326	IL3/FYN/PIK3CD	3
R-HSA-9692914	SARS-CoV-1-host interactions	0.0481 92771	0.0060392 82	0.042753334	SMAD3/CAV1/STING1/SMAD4	4
R-HSA-5684996	MAPK1/MAPK3 signaling	0.0843 37349	0.0061582 17	0.043167893	IL3/FYN/MAPK1/GRIN2B/BRAF/MET/KIT	7
R-HSA-1295596	Spry regulation of FGF signaling	0.0240 96386	0.0065064 49	0.044731838	MAPK1/BRAF	2
R-HSA-1433559	Regulation of KIT signaling	0.0240 96386	0.0065064 49	0.044731838	FYN/KIT	2
R-HSA-1227986	Signaling by ERBB2	0.0361 44578	0.0065817 16	0.044818354	AKT2/FYN/AKT3	3
R-HSA-2173793	Transcriptional activity of SMAD2/SMAD3:SMAD4 heterotrimer	0.0361 44578	0.0069548 52	0.046912447	SMAD3/MAPK1/SMAD4	3
R-HSA-202131	Metabolism of nitric oxide: NOS3 activation and regulation	0.0240 96386	0.0073374 58	0.047263803	NOS3/CAV1	2

SUPPLEMENTARY DATA

R-HSA-432142	Platelet sensitization by LDL	0.0240 96386	0.0073374 58	0.047263803	PECAM1/APOB	2
R-HSA-9022699	MECP2 regulates neuronal receptors and channels	0.0240 96386	0.0073374 58	0.047263803	GRIN2B/MET	2
R-HSA-9659787	Aberrant regulation of mitotic G1/S transition in cancer due to RB1 defects	0.0240 96386	0.0073374 58	0.047263803	CCND1/CDK4	2
R-HSA-9661069	Defective binding of RB1 mutants to E2F1,(E2F2, E2F3)	0.0240 96386	0.0073374 58	0.047263803	CCND1/CDK4	2
R-HSA-9755511	KEAP1-NFE2L2 pathway	0.0481 92771	0.0077431 55	0.049431749	AKT2/AKT3/IDH1/ATF4	4