

Two novel type 2 diabetes loci revealed through integration of TCF7L2 DNA occupancy and SNP association data

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ABSTRACT

Background: The transcription factor 7-like 2 (*TCF7L2*) locus is strongly implicated in the pathogenesis of type 2 diabetes (T2D). We previously mapped the genomic regions bound by *TCF7L2* using ChIP (chromatin immunoprecipitation)-seq in the colorectal carcinoma cell line, HCT116, revealing an unexpected highly significant over-representation of genome-wide association studies (GWAS) loci associated primarily with endocrine (in particular T2D) and cardiovascular traits.

Methods: In order to further explore if this observed phenomenon occurs in other cell lines, we carried out ChIP-seq in HepG2 cells and leveraged ENCODE data for five additional cell lines. Given that only a minority of the predicted genetic component to most complex traits has been identified to date, plus our GWAS-related observations with respect to *TCF7L2* occupancy, we investigated if restricting association analyses to the genes yielded from this approach, in order to reduce the constraints of multiple testing, could reveal novel T2D loci.

Results: We found strong evidence for the continued enrichment of endocrine and cardiovascular GWAS categories, with additional support for cancer. When investigating all the known GWAS loci bound by *TCF7L2* in the shortest gene list, derived from HCT116, the coronary artery disease-associated variant, rs46522 at the *UBE2Z-GIP-ATP5G1-SNF8* locus, yielded significant association with T2D within DIAGRAM. Furthermore, when we analyzed tag-SNPs (single nucleotide polymorphisms) in genes not previously implicated by GWAS but bound by *TCF7L2* within 5 kb, we observed a significant association of rs4780476 within *CPPED1* in DIAGRAM.

Conclusions: ChIP-seq data generated with this GWAS-implicated transcription factor provided a biologically plausible method to limit multiple testing in the assessment of genome-wide genotyping data to uncover two novel T2D-associated loci.

INTRODUCTION

The repertoire of genes already established to play a role in the pathogenesis of type 2 diabetes (T2D) has grown substantially as a consequence of results from recent

Key messages

- Across multiple data sets derived from various cell lines, there is consistent evidence of a highly significant over-representation of genome-wide association study (GWAS)-implicated loci within the list of genes harboring a transcription factor 7-like 2 (*TCF7L2*) occupancy site.
- Given this *TCF7L2* genome-wide occupancy behavior, we observe that through cross-referencing GWAS-derived statistics with specific ChIP (chromatin immunoprecipitation)-seq data, one can facilitate biologically plausible limitations to multiple testing and thus aid gene discovery efforts.
- We reveal *UBE2Z-GIP-ATP5G1-SNF8* and *CPPED1* as novel type 2 diabetes loci using this approach.

genome-wide association studies (GWAS). One of the strongest T2D associations to date, based on risk conferred, is with variation within the transcription factor 7-like 2 (*TCF7L2*) gene.^{1–6} Indeed, the common intronic variant at this locus is strongly associated with the disease in all major racial groups.⁷

In order to better understand the functional role of *TCF7L2*, we previously performed a ChIP (chromatin immunoprecipitation)-seq experiment with this transcription factor to elucidate its binding repertoire genome wide.^{8,9} This approach performed well with the human colorectal carcinoma cell line, HCT116, where the *TCF7L2* protein is abundantly expressed. Unexpectedly, and despite employing a carcinoma cell line, our initial data suggested that the gene list corresponding to *TCF7L2* occupancy sites was strongly enriched for pathway categories related to metabolic-related functions and traits.

To our surprise, we also observed a highly significant over-representation of GWAS-implicated loci within the list of genes harboring a *TCF7L2* occupancy site; indeed, the primary GWAS categories enriched were

for endocrine, in particular T2D, and cardiovascular traits. Our observations are supported by the recent report that classically defined transcription factors operating in the β-cell cluster around variants reported in GWAS.¹⁰

As only a minority of the predicted genetic component to most complex traits has been identified to date, termed the 'missing heritability',¹¹ there is potential for using knowledge of TCF7L2 occupancy to aid further gene discovery for T2D. The rationale behind this is that if one restricted association analyses to just the genes occupied by TCF7L2, one could limit the extent of correction for multiple testing that typically blights GWAS analyses.

In order to elucidate this possibility, we first elected to expand on our initial findings to investigate if this intriguing pattern holds across multiple cell lines, using the algorithm HOMER (Hypergeometric Optimization of Motif EnRichment); indeed, we have already reported our use of this program when analyzing ChIP-seq data for other GWAS-implicated transcription factors, namely MEF2C¹² and FOXA2.¹³ To that end, we meshed our in-house-derived ChIP-seq data sets, both for HCT116 and HepG2, with those made available by the ENCODE project.¹⁴ In addition to analyzing these data sets separately to further investigate possible GWAS locus enrichment, we postulated that many novel genes on the TCF7L2 target list could be relevant to T2D; as such, we analyzed the shortest ChIP-seq-derived gene list, generated in HCT116, in the context of GWAS data itself to investigate if novel T2D loci could be revealed when restricting testing to just the loci derived from this approach.

METHODS

Cell culture and reagent

The HepG2 hepatocarcinoma cell line was purchased from the American Type Cell Center (ATCC, Manassas, Virginia, USA). Cells were cultured at 37°C, 95% humidity, and supplied with 5% CO₂ in ATCC-formulated Eagle's Minimum Essential Medium supplemented with 10% fetal bovine serum (Sigma, St. Louis, Missouri, USA), 2 mM L-glutamine (Gibco Invitrogen, Carlsbad, California, USA), 100 units/mL penicillin/100 µg/mL streptomycin (Cellgro, Manassas, Virginia, USA). On the basis of previous papers outlining TCF7L2 isoforms,^{15–17} we chose from antibodies that were raised to antigen at the most constant region among TCF7L2 isoforms, that is, the amino acids encoded by exons 1–3 (Cat.05-511; Millipore, Billerica, Massachusetts, USA) as described previously.⁸

Chromatin Immunoprecipitation

ChIP was performed in triplicate following the instructions provided by the suppliers of the EZ-ChIP kit (Cat.17-371; Millipore, Billerica, Massachusetts, USA) and as described previously.¹⁸ Cells were sonicated on ice for 12 cycles of 15 s on and 45 s off at setting 3 (2100XL ultrasonic liquid processors, Misonix, Farmingdale,

New York, USA). Sonicated chromatin was primarily in the 100–500 bp range, averaging 200–300 bp.

After overlaying all reads from two independent experiments for HepG2, a total of 3810 binding sites were observed at a false discovery rate of 1%, cumulative Poisson p value of 0.0001, and fold coverage threshold of four times normalized sequence tags in the target experiment comparable with random background sequence tags using the HOMER¹⁹ analysis package. The TCF7L2 ChIP signal was clearly distinct from the pseudo-ChIP signal as identified by GLITR¹⁸ (online supplementary figure S1). In addition, we chose 17 sites with a variable binding score for validation purposes by real-time PCR, all of which showed clear evidence of enrichment (online supplementary figure S2 and table S1).

Sequencing

The sequencing library was prepared as per Illumina's instructions (<http://www.illumina.com>, San Diego, California, USA). Sequencing on the Illumina Genome Analyzer and subsequent analyses were performed at the Functional Genomics Core at the University of Pennsylvania.

DNA libraries were assessed for size, purity, and quantity using an Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, California, USA), followed by sequencing using an Illumina GA-II according to the manufacturer's instructions, and have been described previously.⁸ The ENCODE ChIP-seq ((HepG2, HeLa-S3 (×2), HEK293, MCF7, and PANC1) and input raw sequence files were downloaded from the UCSC database (<http://genome.ucsc.edu/ENCODE/dataMatrix/encodeChipMatrixHuman.html>). HOMER¹⁹ was utilized to determine TCF7L2 binding sites and their association with RefSeq transcripts aligned to hg19 was downloaded from UCSC via HOMER. The candidate target gene was the closest gene regardless of the direction from the binding site. In all cases, the transcription start site of the aligned transcript was used as the anchor point for distance measurements.

TCF7L2 ChIP-seq in ENCODE

We processed the ENCODE TCF7L2 ChIP-seq data for the HepG2, HeLa-S3, HEK293, MCF7, and PANC1 cell lines¹⁴ and also reanalyzed our HCT116 data,⁸ using HOMER.

We observed a wide range in the occupancy site number, location, and nearest unique gene. HCT116 was found to harbor the lowest number of binding sites (n=865) and corresponding genes (n=750). ENCODE's HeLa-S3 (exons 1–3) revealed the highest number of binding sites (n=11 817) and corresponding genes (n=6451; online supplementary table S2).

We elected to reanalyze all of ENCODE's and our own generated TCF7L2 ChIP-seq data with the same HOMER peak parameters described above to eliminate any threshold effects that would be caused by comparing the occupancy sites between different peak finding programs and threshold parameter settings. The number of

placed sequence reads for all eight ChIP-seq experiments varied from a low of 18 139 284 to a high of 57 938 025 (online supplementary table S3).

Pathway analysis

Data were analyzed through the use of Ingenuity Pathways Analysis (Ingenuity Systems, <http://www.ingenuity.com>, Redwood City, California, USA) specified for 'Human'. The genes that corresponded to at least one function or pathway annotation in the Ingenuity Knowledge Base were eligible for the analysis. The p value associated with functions and pathways was calculated using the right-tailed Fisher exact test.

GWAS category analyses

We based our analysis on all GWAS genes summarized in a freeze of the National Human Genome Research Institute (NHGRI) GWAS catalog (<http://www.genome.gov/gwastudies>) from 19 February 2013. Enrichment was investigated using a χ^2 analysis. Our method of scoring overlapping GWAS-implicated genes detected in the ChIP-seq data was to assign 1 point to a GWAS region where all the genes in the region were found in our list and a fraction of a point determine by how many genes were found in our gene list divide by the total genes in the GWAS region. For instance, this analysis model would give a GWAS region with 1 gene the same weight as a region harboring 8 genes.

Association analyses

We derived the list of genes bound by TCF7L2 within 5 kb of the transcription start site in the HCT116 cell line, as it yielded the smallest number of binding sites and thus the smallest list of corresponding genes. First, we derived the list of single nucleotide polymorphisms (SNPs) at GWAS-implicated loci on this gene list (n=40). Furthermore, we aimed to look at the remainder of the gene list, the members of which had not been previously implicated by GWAS, and in order to minimize multiple testing we elucidated which tag-SNPs represented on the basic Illumina Human Hap 550 BeadChip resided with our genes of interest (n=892). We then separately queried both lists against the publicly available GWAS meta-analysis data set generated by DIAGRAM (<http://diagram-consortium.org/downloads.html>)²⁰ to determine if any variants would yield a p value lower than the Bonferroni-corrected p value for the respective test, where the threshold for significance for the previously reported GWAS loci test was set at 1.25×10^{-3} and for the non-GWAS-implicated loci test it was set at 5.61×10^{-5} .

RESULTS

ChIP-seq data appraisal

To extend our previous genomic occupancy analyses for TCF7L2 in HCT116 cells,⁸ we performed ChIP-seq in the human hepatocarcinoma cell line, HepG2, to map DNA sequences bound by TCF7L2. Utilizing HOMER,

the distribution of the binding sites was 1555 intronic, 1920 intergenic, and the remaining 335 in various other genic regions (online supplementary figure S3). We also processed similarly with HOMER TCF7L2 ChIP-seq data for the HepG2, HeLa-S3, HEK293, MCF7, and PANCI cell lines from ENCODE,¹⁴ plus our previously generated HCT116-derived data.⁸

We went on to employ the de novo motif discovery algorithm, also within HOMER, to derive the consensus binding site for these other seven ChIP-seq data sets compared with the consensus motif derived from our HCT116 ChIP-seq data and from previous work by others.²¹ A similar 12 bp consensus was found in 24–53% of all binding sites (online supplementary figure S4). The majority of occupancy (>93%) fell within 5–500 kb of a RefSeq gene transcription start site in the remaining seven ChIP-seq data sets analyzed (online supplementary table S4).

We went on to perform pathway analyses for each of the eight ChIP-seq-derived gene sets. In HCT116, we observed pathways related to 'Factors Promoting Cardiogenesis in Vertebrates', 'Type II Diabetes Mellitus Signaling', and 'NF- κ B Activation by Viruses,' respectively, making them the most significant annotations and readily surviving correction for multiple comparisons (see all categories that achieved a nominal p<0.05 in online supplementary table S5). We also observed that HeLaS3 (exons 1–3), HeLaS3 (exons 4–16), MCF7, and PANCI yielded significant enrichment, following adjustment for multiple comparisons (uncorrected p value: 4.47×10^{-6} , 9.12×10^{-6} , 5.62×10^{-4} , and 9.33×10^{-4}) for genes in the 'Type II Diabetes Mellitus Signaling' category from the top 20 canonical pathway analyses (see all categories that achieved a nominal p<0.05 in online supplementary tables S6–S9). We observed consistent under-representation of members of the β -cell-related pathway in the 'Type II Diabetes Mellitus Signaling' category and over-representation of binding in other tissues within the same category across these data sets (see figure 1 for representative image derived from HCT116 in-house data).

Three of the data sets, two derived from the liver and one from the kidney, that is, two HepG2 and one HEK293, did not yield a significant enrichment of genes in the 'Type II Diabetes Mellitus Signaling' category from the canonical pathway analyses (see all categories that reached a nominal p<0.05 in online supplementary tables S10–S12).

In addition, our pathway analysis also determined consistent and significant enrichment of genes in the 'Wnt/ β -catenin Signaling', 'Molecular Mechanisms of Cancer', and 'Factors Promoting Cardiogenesis in Vertebrates' categories from the top 20 canonical pathway analyses in all eight of the cell lines (see all categories that achieve an adjusted p<0.05 in online supplementary tables S5–S12).

GWAS category enrichment

Given that original HCT116 study suggested TCF7L2 occupancy was found more often at GWAS loci than

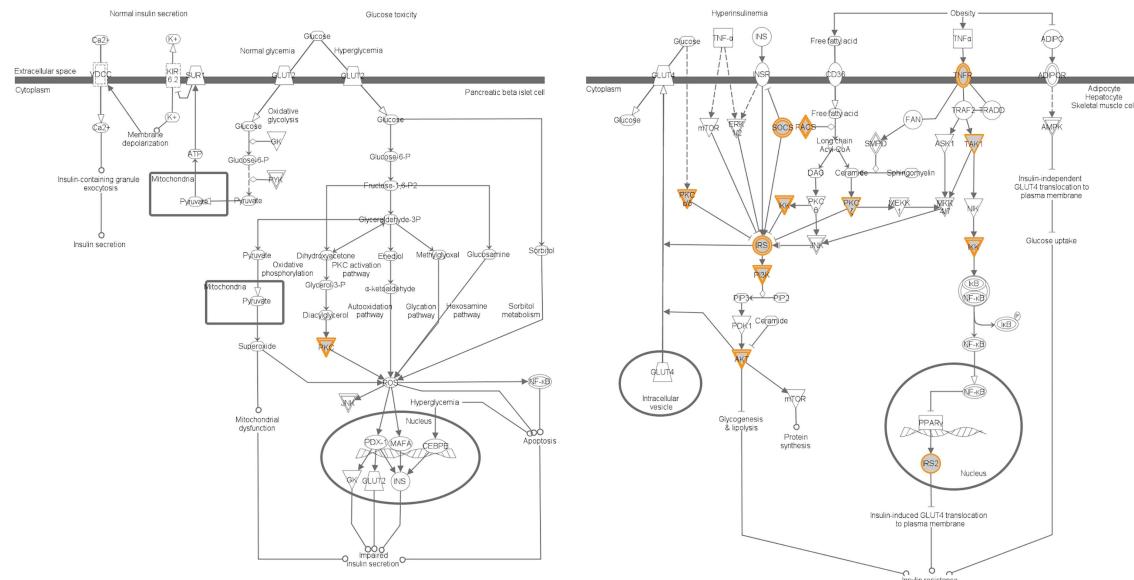


Figure 1 TCF7L2 ChIP-seq in HCT116 cells. The orange color genes in the 'Type II Diabetes Mellitus Signaling' pathway represents TCF7L2 binding sites candidate target genes that were the closest gene transcription start site to TCF7L2 binding sites regardless of the direction from the binding site. Data were analyzed through the use of Ingenuity Pathways Analysis (Ingenuity Systems, <http://www.ingenuity.com>, Redwood City, California, USA) specified for 'Human'. The genes that contain at least one function or pathway annotation in the Ingenuity Knowledge Base were eligible for the analysis. ChIP, chromatin immunoprecipitation; TCF7L2, transcription factor 7-like 2; VDCC, voltage-dependent calcium channels; JNK, Jun N-terminal kinases; ROS, reactive oxygen species; PKC, protein kinase C; NF- κ B, nuclear factor- κ B; SUR, sulfonylurea receptor; TNF α , tumor necrosis factor α ; INS, insulin; IRS, INS receptor; TRAF2, TNF receptor-associated factor 2; mTOR, mechanistic target of rapamycin; SMPD, sphingomyelin phosphodiesterases; DAG, diacylglycerol; PPAR, peroxisome proliferator-activated receptors; GK, glucokinase; PYK, pyruvate kinase; GLUT, glucose transporter; ADIPOR, adiponectin receptor.

expected by chance,⁸ as did our work with MEF2C¹² and FOXA2,¹³ we were motivated to query the results for each data set in turn against all GWAS signals reported, as derived from the NHGRI GWAS catalog.

Of the 2435 nearest genes with a TCF7L2 binding site in our in-house HepG2-generated data set, representing 12.8% of all RefSeq genes used in the overall analysis ($n=19\ 015$), there was a highly significant over-representation of loci implicated in disease susceptibility by GWAS (629.71 of 3607 (17.5%) loci; $p=1.09\times 10^{-10}$; table 1). This observation was primarily driven by excess loci revealed from GWAS of endocrine ($p=6.18\times 10^{-10}$), cardiovascular ($p=9.30\times 10^{-10}$), and cancer ($p=1.04\times 10^{-6}$) traits; specifically, T2D also showed an enrichment ($p=8.80\times 10^{-3}$). In contrast, we observed only marginal or no significant enrichment of GWAS signals for neurological or inflammation-related traits.

Expanding our GWAS signal analyses to the data derived from the other six cell lines (HeLaS3 (exons 1–3), HeLaS3 (exons 4–16), MCF7, Panc1, HCT116, HEK293, and HepG2 (ENCODE)), we determined that there was also highly significant over-representation of GWAS loci for TCF7L2 targets in all seven cell lines (table 1). As seen in HepG2 (in-house), this observation was again primarily driven by excess loci from GWAS of endocrine, cardiovascular, and cancer traits. As demonstrated in HepG2 (in-house), T2D GWAS-implicated loci specifically are also generally enriched, although not statistically significant due to the relatively small

list of GWAS-implicated T2D genes being queried. Neurological and inflammation-related GWAS signals were largely consistently shown to have marginal or no enrichment in the seven ChIP-seq data sets, comparable with what was seen in HepG2 (in-house; table 1).

To contrast with control data sets, we also generated a random list of 5000 genes from the 19 015 RefSeq genes used by HOMER to determine the nearest gene lists described above to ascertain if there was a bias of our data analysis. The randomly generated gene list showed no significant over-representation of GWAS genes in the random gene set; in fact, it showed a trend of under-representation of GWAS genes in the random HOMER gene set, primarily due to the fact that some gene names in the NHGRI GWAS catalog are not RefSeq annotations (online supplementary table S13).

Cross comparisons with genome-wide meta-analysis summary data

Given that only a minority of the predicted genetic component to most complex traits has been identified to date, plus the fact that our GWAS-implicated transcription factor of interest shows consistent statistically significant preferential binding to loci associated with complex traits, we investigated if restricting association analyses to just the genes uncovered from our ChIP-seq approach in order to reduce multiple testing could yield novel loci associated with T2D. When investigating all the known GWAS loci bound within 5 kb by TCF7L2 (most likely to

Table 1 Enrichment of GWAS signals for the nearest RefSeq genes to the TCF7L2 binding site in all eight cell lines

	Percentage of total hg19 gene list	Percentage of ChIP-seq gene list	p Values: χ^2	Percentage of total hg19 gene list	Percentage of ChIP-seq gene list	p Values: χ^2
HCT116: 750 genes						
Endocrine	3.9 (750/19 015)	7.3 (64.66/888)	2.69×10^{-6}	10.1 (1924/19 015)	19.7 (175.34/888)	3.38×10^{-15}
T2D	3.9 (750/19 015)	11.0 (9/82)	0.0025	10.1 (1924/19 015)	21.7 (17.83/82)	0.0024
Cancer	3.9 (750/19 015)	10.7 (35.87/335)	5.81×10^{-9}	10.1 (1924/19 015)	22.0 (73.86/335)	9.17×10^{-10}
Cardiovascular	3.9 (750/19 015)	7.8 (36.19/463)	9.33×10^{-5}	10.1 (1924/19 015)	21.3 (98.41/463)	3.34×10^{-11}
Inflammation	3.9 (750/19 015)	7.2 (37.32/521)	0.00 062	10.1 (1924/19 015)	16.3 (85.1/521)	5.40×10^{-5}
Neuropsychiatric	3.9 (750/19 015)	5.7 (33/584)	0.048	10.1 (1924/19 015)	13.5 (78.67/584)	0.023
All	3.9 (750/19 015)	5.9 (212.25/3607)	5.06×10^{-7}	10.1 (1924/19 015)	15.0 (541.21/3607)	2.58×10^{-14}
HeLa exons (4–16): 1983 genes						
Endocrine	10.4 (1983/19 015)	16.8 (148.86/888)	1.64×10^{-7}	12.8 (2435/19 015)	21.3 (188.73/888)	6.18×10^{-10}
T2D	10.4 (1983/19 015)	17.5 (14.33/82)	0.086	12.8 (2435/19 015)	23.8 (19.5/82)	0.0088
Cancer	10.4 (1983/19 015)	19.8 (62.21/335)	3.41×10^{-5}	12.8 (2435/19 015)	23.7 (79.29/335)	1.04×10^{-6}
Cardiovascular	10.4 (1983/19 015)	20.0 (92.50/463)	9.18×10^{-9}	12.8 (2435/19 015)	24.4 (113.02/463)	9.30×10^{-10}
Inflammation	10.4 (1983/19 015)	14.0 (73.13/521)	0.02	12.8 (2435/19 015)	15.4 (80.43/521)	0.14
Neuropsychiatric	10.4 (1983/19 015)	12.5 (72.94/584)	0.15	12.8 (2435/19 015)	18.2 (106/584)	0.0011
All	10.4 (1983/19 015)	14.0 (506.47/3607)	2.02×10^{-8}	12.8 (2435/19 015)	17.5 (629.71/3607)	1.09×10^{-10}
HEK293: 3519 genes						
Endocrine	18.5 (3519/19 015)	32.5 (288.23/888)	6.46×10^{-16}	20.3 (3863/19 015)	31.9 (283.57/888)	8.36×10^{-11}
T2D	18.5 (3519/19 015)	37.2 (30.5/82)	0.00 057	20.3 (3863/19 015)	36.0 (29.5/82)	0.0053
Cancer	18.5 (3519/19 015)	32.0 (107.19/335)	9.26×10^{-7}	20.3 (3863/19 015)	32.0 (107.09/335)	4.97×10^{-5}
Cardiovascular	18.5 (3519/19 015)	36.6 (169.37/463)	4.74×10^{-14}	20.3 (3863/19 015)	35.6 (164.92/463)	7.28×10^{-10}
Inflammation	18.5 (3519/19 015)	25.9 (134.85/521)	0.00 058	20.3 (3863/19 015)	28.7 (149.47/521)	0.0002
Neuropsychiatric	18.5 (3519/19 015)	31.2 (182.4/584)	1.33×10^{-9}	20.3 (3863/19 015)	25.2 (147/584)	0.022
All	18.5 (3519/19 015)	27.4 (988.25/3607)	1.54×10^{-22}	20.3 (3863/19 015)	28.3 (1019.56/3607)	5.47×10^{-17}
PANC1: 5123 genes						
Endocrine	26.9 (5123/19 015)	34.5 (306.16/888)	0.00 029	33.9 (6451/19 015)	42.0 (372.76/888)	0.00 073
T2D	26.9 (5123/19 015)	44.5 (36.5/82)	0.0087	33.9 (6451/19 015)	47.4 (38.83/82)	0.082
Cancer	26.9 (5123/19 015)	36.5 (122.21/335)	0.0047	33.9 (6451/19 015)	47.9 (160.32/335)	0.00 041
Cardiovascular	26.9 (5123/19 015)	35.1 (162.48/463)	0.0037	33.9 (6451/19 015)	49.9 (230.9/463)	2.13×10^{-6}
Inflammation	26.9 (5123/19 015)	31.1 (161.98/521)	0.12	33.9 (6451/19 015)	38.8 (202.03/521)	0.11
Neuropsychiatric	26.9 (5123/19 015)	29.0 (169.5/584)	0.38	33.9 (6451/19 015)	37.7 (220.2/584)	0.19
All	26.9 (5123/19 015)	30.3 (1094.66/3607)	0.0016	33.9 (6451/19 015)	38.0 (1369.44/3607)	0.0013
HeLa exons (1–3): 6451 genes						
Endocrine	33.9 (6451/19 015)	42.0 (372.76/888)		33.9 (6451/19 015)	47.4 (38.83/82)	
T2D	33.9 (6451/19 015)	47.4 (38.83/82)		33.9 (6451/19 015)	47.9 (160.32/335)	
Cancer	33.9 (6451/19 015)	47.9 (160.32/335)		33.9 (6451/19 015)	49.9 (230.9/463)	
Cardiovascular	33.9 (6451/19 015)	38.8 (202.03/521)		33.9 (6451/19 015)	38.8 (202.03/521)	
Inflammation	33.9 (6451/19 015)	37.7 (220.2/584)		33.9 (6451/19 015)	37.7 (220.2/584)	
Neuropsychiatric	33.9 (6451/19 015)	38.0 (1369.44/3607)		33.9 (6451/19 015)	38.0 (1369.44/3607)	

We based our analysis on all GWAS genes summarized in the NHGRI GWAS catalog (<http://www.genome.gov/gwastudies>) from 19 February 2013. Enrichment was investigated using a χ^2 analysis. Our method of scoring the GWAS ChIP-seq gene overlap was to assign 1 point to a GWAS region where all the genes in the region were found in our list, and a fraction of a point determined by how many genes were found in our gene list divided by the total genes in the GWAS region. This analysis model would equally weight a GWAS region with 1 gene the same as a region with 8 genes as a single region.

ChIP, chromatin immunoprecipitation; GWAS, genome-wide association studies; T2D, type 2 diabetes; TCF7L2, transcription factor 7-like 2.

be functional) in the shortest gene list in order to minimize multiple testing, derived from HCT116, apart from the known *TCF7L2* locus itself (rs7901695), the coronary artery disease-associated variant, the T allele of rs46522 within the *UBE2Z-GIP-ATP5G1-SNF8* locus, yielded significant and novel DIAGRAM-derived association with T2D risk ($OR=1.07$; $p=3.20\times10^{-4}$) (table 2); indeed, the occupancy site was ~ 4 kb from the transcription start site for *GIP* in an intergenic region known to be a hub for binding proteins, H3K27Ac histone marks and open chromatin via a DNase I hypersensitive site. Furthermore, when we analyzed Illumina Human Hap 550 tag-SNPs within genes not previously implicated by GWAS but bound within 5 kb by *TCF7L2* in HCT116, again due to the fact that it was the shortest gene list, we observed significant association within the DIAGRAM data set of the A allele of rs4780476 within the gene encoding calcineurin-like phosphoesterase domain-containing protein 1 (*CPPED1*) with T2D risk ($OR=1.1$, $p=4.10\times10^{-5}$; table 2). Furthermore, the *TCF7L2* occupancy site was in the immediate *CPPED1* promoter region.

DISCUSSION

Given that only a minority of the predicted genetic component to most complex traits has been identified to date, plus the fact that this GWAS-implicated transcription factor shows preferential binding to genes genetically associated with complex traits, we investigated if restricting association analyses to the genes yielded from our ChIP-seq approach in order to reduce multiple testing could yield novel loci associated with T2D. Indeed, we found that of the known GWAS loci for any trait bound by *TCF7L2* within 5 kb in HCT116, the coronary artery disease-associated variant, rs46522, within the *UBE2Z-GIP-ATP5G1-SNF8* locus²² yielded association that survived correction for multiple testing. Interestingly, rs46522 is in strong LD with two potential functional variants in the biologically plausible gene encoding gastric inhibitory polypeptide (*GIP*): p.Ser103Gly (rs2291725) and variant influencing the splice site of intron 3 (rs2291726) leading to a truncated transcript.²² This is particularly notable as this observation implicates a variant playing a role in T2D after being found originally in another GWAS category, i.e. cardiovascular. It has long been thought that *TCF7L2* may confer its T2D effect via incretins,¹ of which *GIP* is one, thus furthering the case for this line of investigation; indeed, the locus encoding the receptor for *GIP* (*GIPR*) has already been reported in relevant GWAS settings to be associated with body mass index^{23–25} and to influence the glucose and insulin responses to an oral glucose challenge.²⁶

Furthermore, when considering the non-GWAS-implicated loci bound by *TCF7L2* within 5 kb in HCT116, we observed significant association with rs4780476 within *CPPED1*. This is an equally interesting observation, as only two papers have been published to date on this gene product, with one showing that

Table 2 DIAGRAM-derived association results for type 2 diabetes with respect to the loci on interest

SNP	CHROMOSOME POSITION	RISK_ALLELE	OTHER_ALLELE	P_VALUE	OR_95%	N_CASES	N_CONTROLS	Gene
rs7901695	10	T	C	2.50E-65	1.37	1.32	1.42	<i>TCF7L2</i> *
rs46522	17	C	T	3.20E-04	1.07	1.03	1.11	<i>UBE2Z-GIP-ATP5G1-SNF8</i>
rs4780476	16	C	A	4.10E-05	1.1	1.05	1.15	<i>CPPED1</i>

Variants previously published for GWAS of any trait
 SNP CHROMOSOME POSITION RISK_ALLELE OTHER_ALLELE P_VALUE OR OR_95% N_CASES N_CONTROLS Gene
 rs7901695 10 T C 2.50E-65 1.37 1.32 1.42 56 862 *TCF7L2**
 rs46522 17 C T 3.20E-04 1.07 1.03 1.11 9580 53 810 *UBE2Z-GIP-ATP5G1-SNF8*
 Variants not previously reported by GWAS of type 2 diabetes
 SNP CHROMOSOME POSITION RISK_ALLELE OTHER_ALLELE P_VALUE OR OR_95% N_CASES N_CONTROLS Gene
 rs4780476 16 C A 4.10E-05 1.1 1.05 1.15 6934 49 977 *CPPED1*

These loci survived correction for multiple testing based on the constraints derived from working with the HCT116 ChIP-seq 5 kb gene list and integrating with tag-SNPs coinciding with genes on that list.
 *Locus previously reported to be associated with type 2 diabetes.
 ChIP, chromatin immunoprecipitation; SNP, single nucleotide polymorphism.

downregulation of *CPPED1* expression improves glucose metabolism in vitro in adipocytes²⁷ and another implicating it in syndromic obesity using array comparative genomic hybridization.²⁸

The challenge of the increasing level of genetic data being generated in population-based cohorts, such as imputed genome-wide genotypes, exome and whole-genome data, is how one can derive true positive signals from the large amount of data, where the required stringent corrections for multiple testing at the genome level can easily miss true signals. Indeed, there have been great efforts to rationalize restricted testing to plausible regions of the genome to address a particular complex trait, most typically by leveraging previously reported linkage signals. However, linkage regions are often broad in terms of genomic regions covered and are therefore fraught with imprecision. Our limitation of multiple testing is based on biological plausibility, where a GWAS-implicated transcription factor is clearly pointing us to genes that are genetically associated with complex disease more often than expected by chance and thus may also be pointing us to novel genes where their strength of the association was at the level of noise at the genome-wide scale.

We carried out the meshing of GWAS-derived data with a ChIP-seq-derived gene list for a GWAS-implicated transcription factor in one of our cell lines. The rationale was that as all cell lines exhibited the same GWAS category enrichment characteristic, we would aim to carry out this investigation by narrowing the field as much as possible. As such, we elected to only leverage the gene names derived from the cell line that yielded the shortest gene list, namely HCT116. We also added the extra constraint of the site being within 5 kb of the nearest gene, as this made them the most biologically plausible, and thus limiting our testing further. We also limited our testing by only considering tag-SNPs used on a conventional genotyping array. Of course, we recognize that these cut-offs are completely arbitrary and that further testing with additional genotype and phenotype (we only considered T2D due to the obvious *TCF7L2* connection) data sets should be the subject of subsequent studies to refine this data-mining approach.

In conclusion, our study has further characterized loci bound by *TCF7L2*, which has in turn reinforced our previous observation that *TCF7L2* has a statistically significant preference to occupy loci previously implicated by GWAS. By cross-referencing the loci at these occupancy sites with GWAS results in order to restrict correction for multiple testing, *UBE2Z-GIP-ATP5G1-SNF8* and *CPPED1* have been uncovered as T2D-associated loci. This approach has potential utility for the discovery process of novel therapeutic targets for diabetes and related traits in the future.

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Contributors JZ, JS, SD, QX, VCG, KHK, ADW, and SFAG generated the data; MEJ, JS, KHK, ADW, and SFAG analyzed the data; and MEJ, JZ, SD, QX, VCG, JS, KHK, ADW, and SFAG reviewed the manuscript and contributed to the writing.

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Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All sequence reads from the ChIP-seq data sets generated at the Children's Hospital of Philadelphia and the University of Pennsylvania are available on request.

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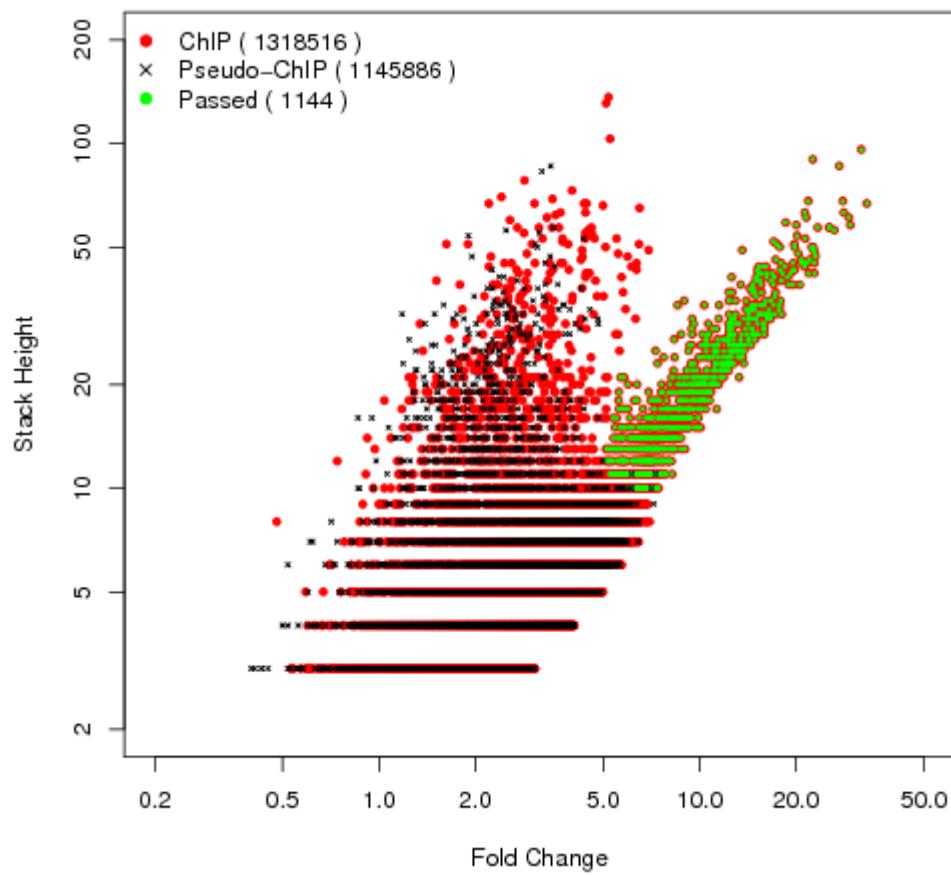
REFERENCES

- Grant SF, Thorleifsson G, Reynisdottir I, et al. Variant of transcription factor 7-like 2 (*TCF7L2*) gene confers risk of type 2 diabetes. *Nat Genet* 2006;38:320–3.
- Sladek R, Rocheleau G, Rung J, et al. A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature* 2007;445:881–5.
- Saxena R, Voight BF, Lyssenko V, et al. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science* 2007;316:1331–6.
- Scott LJ, Mohlke KL, Bonnycastle LL, et al. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science* 2007;316:1341–5.
- Zeggini E, Weedon MN, Lindgren CM, et al. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. *Science* 2007;316:1336–41.
- Voight BF, Scott LJ, Steinhorsdottir V, et al. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. *Nat Genet* 2010;42:579–89.
- Cauchi S, El Achhab Y, Choquet H, et al. *TCF7L2* is reproducibly associated with type 2 diabetes in various ethnic groups: a global meta-analysis. *J Mol Med* 2007;85:777–82.
- Zhao J, Schug J, Li M, et al. Disease-associated loci are significantly over-represented among genes bound by transcription factor 7-like 2 (*TCF7L2*) in vivo. *Diabetologia* 2010;53:2340–6.
- Deliard S, Zhao J, Xia Q, et al. Generation of high quality chromatin immunoprecipitation DNA template for high-throughput sequencing (ChIP-seq). *J Vis Exp* 2013(74):e50286.
- Pasquali L, Gaulton KJ, Rodriguez-Segui SA, et al. Pancreatic islet enhancer clusters enriched in type 2 diabetes risk-associated variants. *Nat Genet* 2014;46:136–43.
- Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. *Nature* 2009;461:747–53.
- Johnson ME, Deliard S, Zhu F, et al. A ChIP-seq-defined genome-wide map of MEF2C binding reveals inflammatory pathways associated with its role in bone density determination. *Calcif Tissue Int* 2014;94:396–402.
- Johnson ME, Schug J, Wells AD, et al. Genome-wide analyses of ChIP-seq derived FOXA2 DNA occupancy in liver points to genetic networks underpinning multiple complex traits. *J Clin Endocrinol Metab* 2014;99:E1580–5.
- Consortium EP, Dunham I, Kundaje A, et al. An integrated encyclopedia of DNA elements in the human genome. *Nature* 2012;489:57–74.

15. Mondal AK, Das SK, Baldini G, et al. Genotype and tissue-specific effects on alternative splicing of the transcription factor 7-like 2 gene in humans. *J Clin Endocrinol Metab* 2010;95:1450–7.
16. Osmark P, Hansson O, Jonsson A, et al. Unique splicing pattern of the TCF7L2 gene in human pancreatic islets. *Diabetologia* 2009;52:850–4.
17. Prokunina-Olsson L, Welch C, Hansson O, et al. Tissue-specific alternative splicing of TCF7L2. *Hum Mol Genet* 2009;18:3795–804.
18. Tuteja G, White P, Schug J, et al. Extracting transcription factor targets from ChIP-Seq data. *Nucleic Acids Res* 2009;37:e113.
19. Heinz S, Benner C, Spann N, et al. Simple combinations of lineage-determining transcription factors prime cis-regulatory elements required for macrophage and B cell identities. *Mol Cell* 2010;38:576–89.
20. Morris AP, Voight BF, Teslovich TM, et al. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat Genet* 2012;44:981–90.
21. Hatzis P, van der Flier LG, van Driel MA, et al. Genome-wide pattern of TCF7L2/TCF4 chromatin occupancy in colorectal cancer cells. *Mol Cell Biol* 2008;28:2732–44.
22. Li Z, Gadue P, Chen K, et al. Foxa2 and H2A.Z mediate nucleosome depletion during embryonic stem cell differentiation. *Cell* 2012;151:1608–16.
23. ENCODE Project Consortium. A user's guide to the encyclopedia of DNA elements (ENCODE). *PLoS Biol* 2011;9:e1001046.
24. Weedon MN, Ellard S, Pringle MJ, et al. An in-frame deletion at the polymerase active site of POLD1 causes a multisystem disorder with lipodystrophy. *Nat Genet* 2013;45:947–50.
25. Speliotes EK, Willer CJ, Berndt SI, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet* 2010;42:937–48.
26. Saxena R, Hivert MF, Langenberg C, et al. Genetic variation in GIPR influences the glucose and insulin responses to an oral glucose challenge. *Nat Genet* 2010;42:142–8.
27. Manning AK, Hivert MF, Scott RA, et al. A genome-wide approach accounting for body mass index identifies genetic variants influencing fasting glycemic traits and insulin resistance. *Nat Genet* 2012;44:659–69.
28. Vuillaume ML, Naudion S, Banneau G, et al. New candidate loci identified by array-CGH in a cohort of 100 children presenting with syndromic obesity. *Am J Med Genet A* 2014;164A:1965–75.

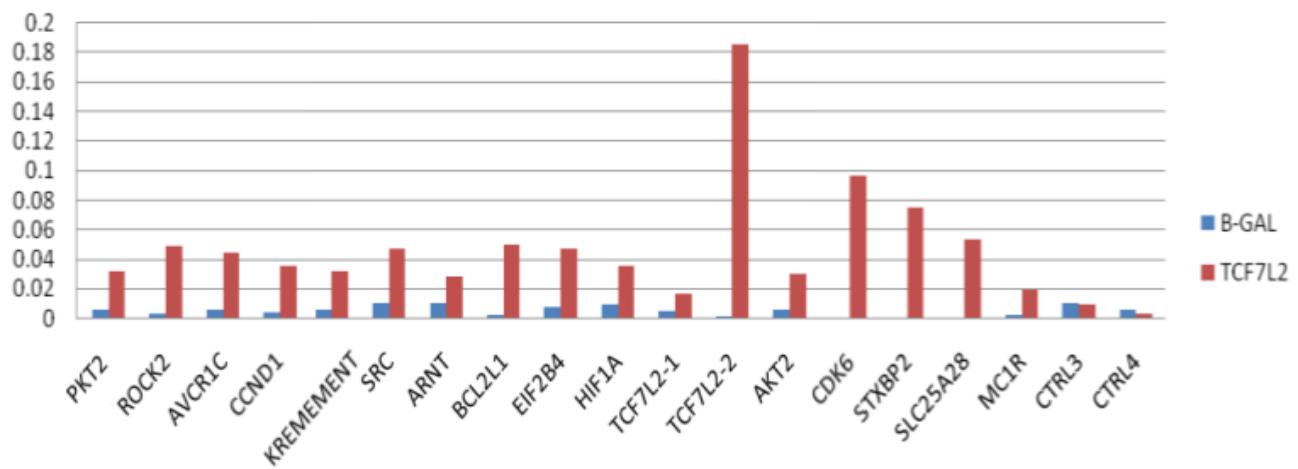
Supplementary Figures:

Supplementary Figure 1: Identification of enriched regions with GLITR. GLITR (GLobal Identifier of Target Regions) accurately identifies enriched regions in target data by calculating a fold-change based on random samples of control (input chromatin) data. It uses a classification method to identify regions in ChIP data that have a peak height and fold-change which do not resemble regions in an input sample. The red dots indicate the stack height and fold-change (relative to a pool of human input sequence) of regions identified in TCF7L2 ChIP material from HepG2 cells. The black points are for an equal number of reads sampled from the human input pool. Green dots indicate regions that are significantly different (with an FDR=1%) from the distribution of pooled input regions. Significant regions in the TCF7L2 ChIP were then removed if they overlapped with a region from the HepG2 input sample. Encircled data-points represent distinct signals over background.



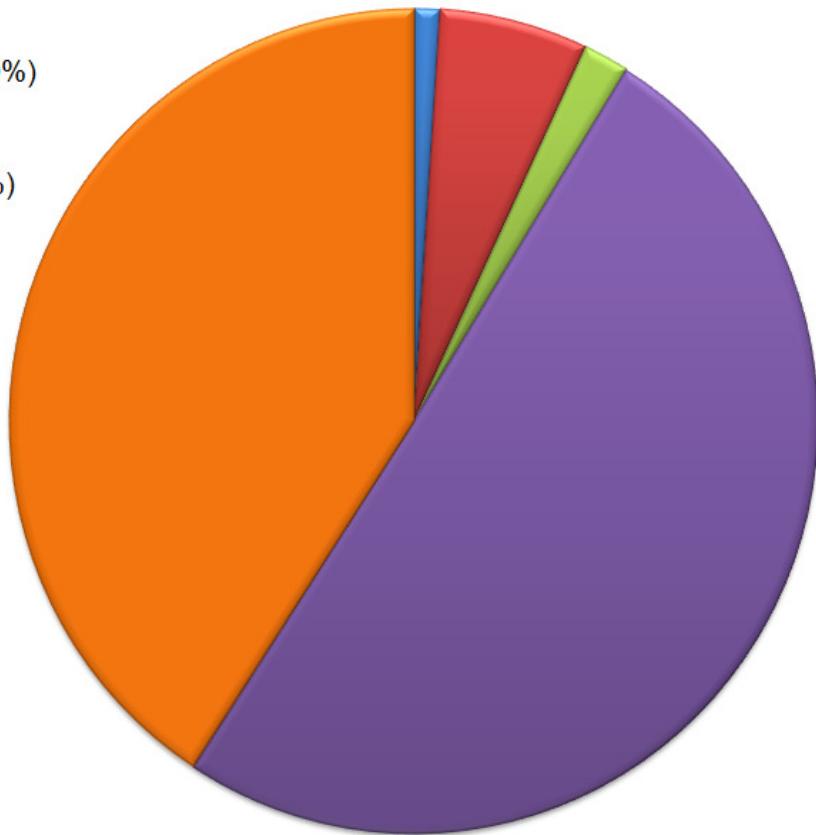
Supplementary Figure 2: Validation results for selected HepG2 TCF7L2 binding sites using quantitative PCR. TCF7L2 binding sites with varying binding strength score were selected to further assess the reliability of ChIP-seq data using real time quantitative PCR. ChIPs were carried out using anti-TCF7L2 (Millipore Cat. 05-511) plus anti- β -galactosidase (Promega Cat. Z378B) as a control in HCT116 cells. One percent of chromatin of each IP was used as Input, of which 50 fold dilution was then used in the PCR. Subsequently, quantitative real time PCR was performed on the ABI 7900 instrument. S.D. are plotted (n=3).

Validation of TCF7L2 binding in HepG2 cells



Supplementary Figure 3: Genomic distribution of TCF7L2 binding sites in the HepG2 in house cell line. Two independent TCF7L2 ChIP-seq experiments in HepG2 experiments generated a total of 3,810 binding sites were observed at a false discovery rate of 1% using HOMER. The majority of binding sites were determined to be located in intergenic and intronic regions.

- UTR: 39 (1.0%)
- Promoter-TSS: 226 (5.9%)
- Exon: 70 (1.8%)
- Intergenic: 1,920 (50.4%)
- Intron: 1,555 (40.8%)



Supplementary Figure 4: Overall 12bp consensus motif generated from nucleotide distribution for the *in vivo* TCF7L2 binding pattern. We employed the *de novo* motif discovery algorithm within HOMER to derive the consensus binding site for all 8 cell lines as indicated below.

HepG2 (In house): defined by HOMER ($P=1.0 \times 10^{-1,278}$). 12bp consensus found in 47.4%.
HEPG2 (ENCODE) defined by HOMER ($P=1.0 \times 10^{-1,053}$). 12bp consensus found in 53.7%.
HeLaS3 (exon 4-16) defined by HOMER ($P=1.0 \times 10^{-736}$). 12bp consensus found in 43.7%.
HeLaS3 (exon 1-3) defined by HOMER ($P=1.0 \times 10^{-1,325}$). 12bp consensus found in 24.3%.
HEK293 defined by HOMER ($P=1.0 \times 10^{-1,101}$). 12bp consensus found in 34.1%.
MCF7 defined by HOMER ($P=1.0 \times 10^{-1,129}$). 12bp consensus found in 34.6%.
PANC1 defined by HOMER ($P=1.0 \times 10^{-1,208}$). 12bp consensus found in 34.6%.
HCT116 (in house) defined by HOMER ($P=1.0 \times 10^{-358}$). 12bp consensus found in 50.6%.



Supplementary Table 1: Primer sequence used in real-time PCR for binding site validation

Gene	Region (hg19)	Primer
<i>TCF7L2</i>	chr10:114709983-114710213	TCGCCCTGTCAATAATCTCC AGCCGAAGATAACAGGAGGTG
<i>TCF7L2</i>	chr10:114767138-114767346	CACTCTTTGGCCAGGAT GCAGCACAAACCTTCAGTCAA
<i>AKT2</i>	chr19:40791541-40791706	AGGGCCTAGCCGTAGTGATT TGACGAGCACACTGAAAAGG
<i>CDK6</i>	chr7:92464789-92465012	GCTGGCTGAATGTGACTTGA AGAGGCGCATGAAGGATT
<i>STXBP</i>	chr19:7716981-7717399	CAATTCCCGGTTCTTGA GTGCTCGTTAGGACCCGATA
<i>SLC25A28</i>	chr10:101380154-101380513	AAGCAACCATTGGTGGAGAC AGTTTCTCCGCCCTTCTAA
<i>MC1R</i>	chr16:89984343-89984643	CTTTGATGTGGCTGTTGGTG GACCCTCCAGTCATCTCGTC
<i>KREMEN1</i>	chr22:29492710-29492920	TGCTTTCAATATGGTTTGACAT TGTCGGGTGTCAGTTGAGAA
<i>SRC</i>	chr20:35968893-35969121	CAGCTCTAGCTGCAGATTCC GAAGAGGCCAGAGAAGGAC
<i>ACVR1C</i>	chr2:158485181-158485339	CTGCGAGCAGCAGGAGAG CCACACTGACTAGAGCCAACC
<i>CCND1</i>	chr11:69455838-69455977	CACACGGACTACAGGGGAGT TCGGCTCTCGCTTGCT
<i>ARNT</i>	chr1:150848622-150848871	ACCACATCACAGACCAGACG GGGGACTTGGTAGACTCG
<i>BCL2L1</i>	chr20:30292494-30292743	CTGCCTCTGTGTGGAAGTT ATCGACCAGTTCTGTAGGC
<i>EIF2B4</i>	chr2:27592794-27593158	AAACAGGGCACAAAGTGAGC GGCTCCGGTCTACACAGTCT
<i>HIF1A</i>	chr14:62181845-62182017	TGGGAGTATAGACTGAATTACCATCTT AAATCCAAAATCTTAAC TGAAAGG
<i>PKT2</i>	chr1:204462725-204462945	CCTCTCCCACAATCCAGAA GCTGCTCTCCTGGCCTATAC
<i>ROCK2</i>	chr2:11497557-11498080	GTGTCGGCTCCTCTGATCTC GGCATGTCTGGATGACCTCT
<i>CTRL3</i>	chr1:152285711-152285766	ATGTGGTGTGGCTGTGATGGGAAC CGAGCAATCGGTAATAGGTCTGG
<i>CTRL4</i>	chr7:159488-159583	CTTGCCCCCTCTATTCCCCACCAAC CCCCCTCCCATCACTCACTGTCC

Supplementary Table 2: TCF7L2 binding site and nearest unique genes analysis: by HOMER in all 8 ChIP-seq experiments. HOMER was utilized to determine TCF7L2 binding sites and their association with RefSeq transcripts aligned to hg19 downloaded from UCSC via HOMER. The candidate target gene was the closest gene regardless of direction from binding site and TSS of ReSeq transcript.

<u>Cell Line: TCF7L2 ChIP-seq</u>	<u>Binding Sites</u>	<u>Unique Genes</u>
HCT116 (in-house)	864	750
HEPG2: (ENCODE)	2,745	1,924
HeLaS3 Exon (4-16)	2,440	1,983
HEPG2 (in-house)	3,810	2,435
HEK293	6,303	3,519
MCF7	6,013	3,863
PANC1	8,632	5,123
<u>HeLaS3 Exon (1-3)</u>	<u>11,817</u>	<u>6,451</u>

Supplementary Table 3: The number of placed sequence reads for all eight ChIP-seq experiments plus subsequent occupancy sites determined.

Cell Line	Number of sequence read tags mapped (hg19)	Occupancy sites
HCT116 (in house)	18,139,284	864
HEPG2 (in house)	28,787,589	3,810
HEPG2 (ENCODE)	43,397,093	2,745
PANC1 (ENCODE)	32,477,306	8,632
MCF7 (ENCODE)	44,105,603	6,013
Helas3 exon 1-3 (ENCODE)	57,938,025	11,817
Helas3 exon 4-16 (ENCODE)	25,608,903	2,440

Supplementary Table 4: TCF7L2 binding site events that fall within 5kb-500kb of a RefSeq gene. In all cases the TSS of the aligned transcript was used as the anchor point for distance measurements. HOMER was utilized to perform the distance measurements.

Distance from TCF7L2 bind site	HepG2 (In house)	HeLaS3 (exon 1-3)	HeLaS3 (exon4-16)	MCF7
5kb	(503/3,810) 13.2%	(3,611/11,817) 30.6%	(735/2,440) 30.9%	(1,054/6,013) 17.5%
50kb	(1,894/3,810) 49.7%	(7,726/11,817) 65.4%	(1,492/2,440) 61.1%	(3,287/6,013) 54.6%
100kb	(2,516/3,810) 66.0%	(9,357/11,817) 79.2%	(1,874/2,440) 76.8%	(4,328/6,013) 72.0%
500kb	(3,526/3,810) 92.5%	(11,494/11,817) 97.2%	(2,355/2,440) 96.5%	(5,740/6,013) 95.5%
PANC1	HCT116	HEPG2 (ENCODE)	HEK293	
5kb	(3,079/8,632) 35.7%	(323/864) 37.4%	(333/2,745) 12.1%	(1,106/6,303) 17.5%
50kb	(5,684/8,632) 65.8%	(456/864) 52.8%	(1,502/2,745) 54.7%	(3,034/6,303) 48.1%
100kb	(6,776/8,632) 78.5%	(621/864) 71.9%	(2,014/2,745) 73.4%	(4,041/6,303) 64.1%
500kb	(8,307/8,632) 96.2%	(831/864) 96.2%	(2,632/2,745) 95.8%	(5,881/6,303) 93.3%

Supplementary Table 5: All HCT116 TCF7L2 Ingenuity Conical pathways with at least nominal $P < 0.05$

Canonical Pathways	P-value	B-H Multipole testing correction p-value	Molecules
Factors Promoting Cardiogenesis in Vertebrates	1.47911E-05	0.003548134	BMP4,WNT3,SMAD5,PRKCZ,NOG,TGFBR2,MAP3K7,PRKCE,PRKCH,BMP7,DKK1,BMP6,PRKD1,TCF7L2
Type II Diabetes Mellitus Signaling	1.94984E-05	0.003548134	PIK3C2B,SOCS1,AKT2,PIK3R1,SOCS6,IKBKE,PRKCZ,MAP3K7,PIK3CG,SH2B2,ACSL5,PRKCE,IRS2,PRKCH,TNFRSF1B,PRKD1
NF- κ B Activation by Viruses	4.7863E-05	0.003548134	PIK3C2B,AKT2,PIK3CG,PIK3R1,ITGA6,PRKCE,IKBKE,PRKCH,ITGB5,PRKCZ,PRKD1,ITGB3
HER-2 Signaling in Breast Cancer	7.24436E-05	0.005248075	PIK3C2B,AKT2,PIK3CG,PIK3R1,CDK6,PRKCE,PRKCH,ITGB5,PRKCZ,PRKD1,EGFR,ITGB3
VDR/RXR Activation	9.33254E-05	0.005248075	YY1,CYP24A1,PPARD,RUNX2,PRKCE,KLK6,PRKCH,NCOR2,SEM A3B,KLF4,PRKCZ,PRKD1
Xenobiotic Metabolism Signaling	0.000109648	0.005248075	PIK3R1,ABC2,MAF,ALDH1L1,CHST15,PRKCZ,ARNT,MAP3K7,PIK3CG,CHST2,BMP4,WNT3,PIK3R1,TAB2,CSNK1A1,WNT16,IKBKE,MAP3D5,ITGB3,MAP3K7,RUNX2,PIK3CG,MAP3K12,HSP90AA1,PRKCH,NCOR2,NRIP1,NDST1
Growth Hormone Signaling	0.000114815	0.005248075	SOCS1,PIK3C2B,GHR,PIK3CG,PIK3R1,SOCS6,PRKCE,PRKCH,P,PRKCZ,ONECUT1,PRKD1
Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis	0.000114815	0.005248075	PIK3C2B,AKT2,BMP4,WNT3,PIK3R1,TAB2,CSNK1A1,WNT16,IKBKE,MAP3D5,ITGB3,MAP3K7,RUNX2,PIK3CG,MAP3K12,BMP7,DKK1,SFRP1,TNFRSF1B,BMP6,PPP3CA,TCF7L2
Human Embryonic Stem Cell Pluripotency	0.000158489	0.005248075	PIK3C2B,AKT2,BMP4,WNT3,PIK3R1,SMAD3,SMAD7,WNT16,SMA5,NOG,TGFBR2,NTRK3,PIK3CG,BMP7,BMP6,TCF7L2
Wnt/ β -catenin Signaling	0.000234423	0.006456542	GJA1,AXIN2,AKT2,WNT3,PPARD,CSNK1A1,WNT16,BCL9,MYC,T,GFBR2,SOX9,MAP3K7,TLE3,BTRC,PPP2R2C,DKK1,SFRP1,TCF7L2
RANK Signaling in Osteoclasts	0.000239883	0.008128305	MAP3K12,MAP3K9,PIK3C2B,AKT2,MITF,MAP3K7,PIK3CG,PIK3R1,TAB2,NFATC2,IKBKE,PPP9CA
Virus Entry via Endocytic Pathways	0.000338844	0.008128305	PIK3C2B,HLA-A,PIK3CG,PIK3R1,ITGA6,PRKCE,PRKCH,CXADR,ITGB5,PRKCZ,PRKD1,ITGB3
Thrombopoietin Signaling	0.000436516	0.01023293	MYC,PIK3C2B,PIK3CG,PIK3R1,PRKCE,IRS2,PRKCH,PRKCZ,PRKD1
Chronic Myeloid Leukemia Signaling	0.000457088	0.012022644	TGFBR2,MYC,BCL2L1,PIK3C2B,AKT2,HDAC4,PIK3CG,PIK3R1,SMAD3,MAP3K7,IKBKE
LPS-stimulated MAPK Signaling	0.000912011	0.012022644	PIK3C2B,ATF1,MAP3K7,PIK3CG,PIK3R1,PRKCE,IKBKE,PRKCH,P,PRKCZ,PRKD1
Prolactin Signaling	0.000912011	0.020892961	MYC,SOCS1,PIK3C2B,PIK3CG,PIK3R1,SOCS6,PRKCE,PRKCH,P,PRKCZ,PRKD1
Huntington's Disease Signaling	0.001819701	0.020892961	NEUROD1,PIK3C2B,GRIN2B,AKT2,HDAC4,VT1A,PIK3R1,PRKCH,BCL2L1,DYNC1I2,CPLX2,PIK3CG,PRKCE,PRKCH,NCOR2,DNAJ1,B1,GOSR2,PRKD1,EGFR
Erythropoietin Signaling	0.001862087	0.034673685	SOCS1,PIK3C2B,AKT2,PIK3CG,PIK3R1,PRKCE,PRKCH,PRKCZ,P,PRKD1
Role of JAK2 in Hormone-like Cytokine Signaling	0.001905461	0.034673685	SOCS1,GHR,SOCS6,SH2B2,PTPN1,IRS2
Molecular Mechanisms of Cancer	0.001995262	0.034673685	SHH,BMP4,SMAD3,PIK3R1,TAB2,SMAD5,HIF1A,PRKCZ,TGFBR2,MYC,MAP3K7,BCB3,PIK3CG,PRKCE,PRKD1,PIK3C2B,AKT2,SMA D7,CDK6,BCL2L1,RBPJ,BMP7,PRKCH,BMP6,GNAL,BCL2L11
Macropinocytosis Signaling	0.002089296	0.034673685	PIK3C2B,PIK3CG,PIK3R1,PRKCE,PRKCH,ITGB5,PRKCZ,PRKD1,ITGB3
Mouse Embryonic Stem Cell Pluripotency	0.002089296	0.034673685	MYC,PIK3C2B,AKT2,ID2,BMP4,LIF,MAP3K7,PIK3CG,PIK3R1,SMA D5,TCF7L2
ErbB4 Signaling	0.002818383	0.034673685	PIK3C2B,PIK3CG,PIK3R1,YAP1,PRKCE,PRKCH,PRKCZ,PRKD1
IL-3 Signaling	0.002818383	0.039810717	PIK3C2B,AKT2,PIK3CG,PIK3R1,PRKCE,PRKCH,PRKCZ,PPP3CA,PRKD1
HGF Signaling	0.002884032	0.039810717	MAP3K12,MAP3K9,PIK3C2B,AKT2,MAP3K7,PIK3CG,PIK3R1,PRKCE,PRKCH,PRKCZ,PRKD1
CDP-diacylglycerol Biosynthesis I	0.002884032	0.039810717	GPAM,CDS1,MBOAT2,AGPAT3
TR/RXR Activation	0.002951209	0.039810717	PIK3C2B,AKT2,LDLR,COL6A3,SLC2A1,PIK3CG,PIK3R1,NCOR2,H IF1A,TBL1XR1
Phosphatidylglycerol Biosynthesis II (Non-plastidic)	0.003715352	0.039810717	GPAM,CDS1,MBOAT2,AGPAT3
Docosahexaenoic Acid (DHA) Signaling	0.005370318	0.048977882	BCL2L1,PIK3C2B,AKT2,PIK3CG,PIK3R1,APP
Glioma Signaling	0.006025596	0.067608298	PIK3C2B,AKT2,PIK3CG,PIK3R1,CDK6,PRKCE,PRKCH,PRKCZ,PRKD1,EGFR
Role of NANOG in Mammalian Embryonic Stem Cell Pluripotency	0.006025596	0.072443596	PIK3C2B,AKT2,BMP4,LIF,WNT3,PIK3CG,PIK3R1,WNT16,BMP7,S MAD5,BMP6
JAK/Stat Signaling	0.00676083	0.072443596	BCL2L1,SOCS1,PIK3C2B,AKT2,PIK3CG,PIK3R1,SOCS6,PTPN1
Telomerase Signaling	0.007079458	0.077624712	MYC,PIK3C2B,AKT2,HDAC4,PIK3CG,PIK3R1,HSP90AA1,PPP2R2 C,TERF1,EGFR
Amyotrophic Lateral Sclerosis Signaling	0.007585776	0.077624712	GRIN2B,BCL2L1,PIK3C2B,CACNA1D,GRID1,GRIK4,GDNF,PIK3C G,PIK3R1,PPP3CA
TGF- β Signaling	0.007943282	0.081283052	TGFBR2,BMP4,MAP3K7,RUNX2,SMAD3,SMAD7,BMP7,SMAD5,T GIF1
Basal Cell Carcinoma Signaling	0.008912509	0.083176377	SHH,BMP4,GLI2,WNT3,WNT16,BMP7,BMP6,TCF7L2

NF- κ B Signaling	0.008912509	0.087096359	TGFBR2,PIK3C2B,AKT2,GHR,BMP4,MAP3K7,NTRK3,PIK3CG,PIK3R1,TAB2,BTRC,TNFRSF1B,PRKCZ,EGFR
Small Cell Lung Cancer Signaling	0.009549926	0.087096359	MYC,BCL2L1,PIK3C2B,AKT2,PIK3CG,PIK3R1,CDK6,IKBKE
PEDF Signaling	0.009549926	0.087096359	BCL2L1,PIK3C2B,AKT2,GDNF,PIK3CG,PIK3R1,IKBKE,ZEB1
mTOR Signaling	0.01	0.087096359	PIK3C2B,AKT2,PIK3R1,FKBP1A,HIF1A,PRR5L,PRKCZ,DGKZ,RPS24,PP2R2C,PIK3CG,PRKCE,PPP2R2C,PRKCH,PRKD1
Neuregulin Signaling	0.01	0.087096359	MYC,AKT2,PIK3R1,PRKCE,HSP90AA1,PRKCH,PRKCZ,PRKD1,EGR1
Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	0.01023293	0.087096359	SOC51,PIK3C2B,AKT2,WNT3,PIK3R1,CSNK1A1,WNT16,IKBKE,PDK2,MYC,MAP3K7,PIK3CG,PRKCE,NFATC2,PRKCH,DKK1,SFRP1,TNFRSF1B,PPP3CA,TGF β 2,PRKD1
IL-8 Signaling	0.010471285	0.087096359	PIK3C2B,AKT2,ANGPT2,PIK3R1,IKBKE,PRKCZ,ITGB3,RAB11FIP2,BCL2L1,PIK3CG,PRKCE,PRKCH,PRKD1,ITGB5,EGFR
BMP signaling pathway	0.010471285	0.087096359	BMP4,MAP3K7,RUNX2,SMAD7,BMP7,SMAD5,BMP6,NOG
p70S6K Signaling	0.010964782	0.087096359	PIK3C2B,AKT2,PIK3CG,SYK,PIK3R1,PRKCE,PPP2R2C,PRKCH,PRKCZ,PRKD1,EGFR
PTEN Signaling	0.010964782	0.087096359	TGFBR2,BCL2L1,AKT2,GHR,NTRK3,PIK3CG,PIK3R1,IKBKE,BCL2L1,PRKCZ,EGFR
Triacylglycerol Biosynthesis	0.011481536	0.087096359	PPAPDC1A,GPAM,MBOAT2,ELOVL1,AGPAT3
Axonal Guidance Signaling	0.011748976	0.087096359	MMP21,SHH,RGS3,BMP4,GLI2,WNT3,PIK3R1,WNT16,PRKCZ,PIK3CG,ADAM19,PRKCE,SEMA3B,PPP3CA,PRK1,PIK3C2B,NGEF,AKT2,ADAMTS9,SEMA3A,NTRK3,SEMA4G,NFATC2,BMP7,PRKCZ,H,BMP6,EPHA2,GNAL
RAR Activation	0.012022644	0.087096359	AKT2,RDH10,PIK3R1,SMAD3,SMAD7,SMAD5,PRKCZ,SMARCA2,PIK3CG,PRKCE,PRKCH,NRIP1,NCOR2,PRKD1
nNOS Signaling in Neurons	0.012022644	0.087096359	GRIN2B,PRKCE,PRKCH,PRKCZ,PPP3CA,PRKD1
Nitric Oxide Signaling in the Cardiovascular System	0.012302688	0.087096359	PIK3C2B,PIK3C2B,AKT2,CACNA1D,GUCY1A3,PIK3CG,PIK3R1,CSNK1A1,PRKCE,P90AA1
Gap Junction Signaling	0.012302688	0.087096359	PIK3C2B,AKT2,SP3,GUCY1A3,PIK3CG,PIK3R1,CSNK1A1,PRKCE,PRKCH,PRKD1,PPP3CA,PRKCZ,EGFR
Role of JAK1 and JAK3 in γ c Cytokine Signaling	0.012589254	0.087096359	SOC51,PIK3C2B,PIK3CG,SYK,PIK3R1,SH2B2,IRS2
VEGF Family Ligand-Receptor Interactions	0.014125375	0.087096359	PIK3C2B,AKT2,PIK3CG,PIK3R1,PRKCE,PRKCH,PRKCZ,PRKD1
PI3K Signaling in B Lymphocytes	0.014454398	0.09332543	AKT2,ATF1,PIK3CG,SYK,PIK3R1,SH2B2,NFATC2,IKBKE,IRS2,PRKCZ,PPP3CA
Role of Tissue Factor in Cancer	0.014454398	0.09332543	BCL2L1,PIK3C2B,AKT2,PIK3CG,PIK3R1,ITGA6,F3,ITGB5,EGFR,ITGB3
Pyridoxal 5'-phosphate Salvage Pathway	0.014791084	0.09332543	MAP3K9,AKT2,CDK6,CSNK1A1,PRKCE,GRK5,PRKCH
GM-CSF Signaling	0.014791084	0.09332543	RUNX1,BCL2L1,PIK3C2B,AKT2,PIK3CG,PIK3R1,PPP3CA
Acute Myeloid Leukemia Signaling	0.015488166	0.09332543	RUNX1,KITLG,MYC,PIK3C2B,AKT2,PIK3CG,PIK3R1,TCF7L2
Fcy Receptor-mediated Phagocytosis in Macrophages and Monocytes	0.016218101	0.095499259	AKT2,PIK3CG,SYK,PIK3R1,PRKCE,PRKCH,PRKCZ,PRKD1
Role of NFAT in Cardiac Hypertrophy	0.016595869	0.097723722	PIK3C2B,AKT2,HDAC4,LIF,PIK3R1,CSNK1A1,PRKCE,TGFBR2,MAP3K7,PIK3CG,PRKCE,PRKCH,PRKD1,PPP3CA
Ceramide Signaling	0.017782794	0.1	PIK3C2B,AKT2,PIK3CG,PIK3R1,PPP2R2C,TNFRSF1B,PRKCZ,KS1
Production of Nitric Oxide and Reactive Oxygen Species in Macrophages	0.019054607	0.104231743	MAP3K9,PIK3C2B,AKT2,PIK3R1,IKBKE,PRKCZ,MAP3K12,MAP3K7,PIK3CG,PRKCE,PRKCH,PPP2R2C,TNFRSF1B,PRKCZ,PRKD1
G _q Signaling	0.019054607	0.109395637	HRH1,PIK3C2B,AKT2,PIK3CG,PIK3R1,PRKCE,NFATC2,IKBKE,PRKCZ,PRKD1,PPP3CA
Hereditary Breast Cancer Signaling	0.019498446	0.109395637	FANCE,PIK3C2B,AKT2,GADD45B,HDAC4,SMARCA2,PIK3CG,PIK3R1,CDK6,RFC3
IL-2 Signaling	0.022908677	0.109395637	SOC51,PIK3C2B,AKT2,PIK3CG,SYK,PIK3R1
Thioredoxin Pathway	0.023442288	0.127350308	TXNDC2,NXN
Selenocysteine Biosynthesis II (Archaea and Eukaryotes)	0.023442288	0.127350308	SARS,PSTK
Salvage Pathways of Pyrimidine Ribonucleotides	0.024547089	0.127350308	MAP3K9,AKT2,CDK6,CSNK1A1,PRKCE,GRK5,PRKCH,UCK2
Lymphotxin β Receptor Signaling	0.025118864	0.130918192	BCL2L1,PIK3C2B,AKT2,PIK3CG,PIK3R1,IKBKE
Renal Cell Carcinoma Signaling	0.025703958	0.13121999	PIK3C2B,AKT2,SLC2A1,PIK3CG,PIK3R1,HIF1A,ARNT
ErbB Signaling	0.02630268	0.13121999	PIK3C2B,PIK3CG,PIK3R1,PRKCE,PRKCH,PRKCZ,PRKD1,EGFR
P2Y Purinergic Receptor Signaling Pathway	0.026915348	0.133352143	MYC,PIK3C2B,AKT2,PIK3CG,PIK3R1,PRKCE,PRKCH,PRKCZ,PRKD1,ITGB3
Melanoma Signaling	0.030199517	0.134586035	PIK3C2B,AKT2,MTIF,PIK3CG,PIK3R1
G Beta Gamma Signaling	0.031622777	0.150660707	AKT2,PIK3CG,PRKCE,PRKCH,PRKCZ,GNAL,PRKD1,EGFR
B Cell Receptor Signaling	0.031622777	0.153108746	MAP3K12,BCL2L1,MAP3K9,PIK3C2B,AKT2,MAP3K7,PIK3CG,SYK,PIK3R1,NFATC2,IKBKE,PPP3CA
Calcium-induced T Lymphocyte Apoptosis	0.033884416	0.153108746	PRKCE,NFATC2,PRKCH,PRKCZ,PPP3CA,PRKD1
Myc Mediated Apoptosis Signaling	0.033884416	0.158124804	MYC,PIK3C2B,AKT2,PIK3CG,PIK3R1,PRKCE
NGF Signaling	0.034673685	0.158124804	MAP3K12,MAP3K9,PIK3C2B,AKT2,MAP3K7,PIK3CG,PIK3R1,IKBKE,PRKCZ
Dopamine-DARPP32 Feedback in cAMP Signaling	0.034673685	0.158124804	GRIN2B,CACNA1D,KCNJ2,ATF1,GUCY1A3,CSNK1A1,PRKCE,PPP2R2C,PRKCH,PRKCZ,PPP3CA,PRKD1
fMLP Signaling in Neutrophils	0.036307805	0.158124804	PIK3C2B,PIK3CG,PIK3R1,PRKCE,NFATC2,PRKCH,PRKCZ,PPP3CA,PRKD1
NRF2-mediated Oxidative Stress Response	0.036307805	0.161435856	DNAJB8,PIK3C2B,ABCC2,PIK3R1,MAF,PRKCE,MAP3K7,PIK3CG,PRKCE,PRKCH,DNAJB1,FKBP5,PRKD1

Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses	0.037153523	0.161435856	PIK3C2B,PIK3CG,SYK,PIK3R1,PRKCE,PRKCH,PRKCZ,PRKD1
Cardiomyocyte Differentiation via BMP Receptors	0.03801894	0.163681652	BMP4,MAP3K7,BMP7
Natural Killer Cell Signaling	0.03801894	0.163681652	PIK3C2B,AKT2,PIK3CG,SYK,PIK3R1,PRKCE,PRKCH,PRKCZ,PRKD1
Fc Epsilon RI Signaling	0.039810717	0.163681652	PIK3C2B,AKT2,PIK3CG,SYK,PIK3R1,PRKCE,PRKCH,PRKCZ,PRKD1
S-methyl-5'-thioadenosine Degradation II	0.041686938	0.170215851	MTAP
Thiamin Salvage III	0.041686938	0.172186857	TPK1
ILK Signaling	0.041686938	0.172186857	MYC,PIK3C2B,AKT2,PIK3CG,PIK3R1,SH2B2,MYH3,MYH9,IRS2,PP2R2C,HIF1A,ITGB5,ITGB3
IL-15 Signaling	0.042657952	0.172186857	BCL2L1,PIK3C2B,AKT2,PIK3CG,SYK,PIK3R1
CD40 Signaling	0.045708819	0.172186857	PIK3C2B,ATF1,MAP3K7,PIK3CG,PIK3R1,IKBKE
Reelin Signaling in Neurons	0.047863009	0.18238957	MAP3K9,PIK3C2B,PIK3CG,PIK3R1,ITGA6,APP,ITGB3
IL-17A Signaling in Airway Cells	0.047863009	0.187068214	PIK3C2B,AKT2,MAP3K7,PIK3CG,PIK3R1,IKBKE
PKCθ Signaling in T Lymphocytes	0.048977882	0.187068214	MAP3K12,MAP3K9,PIK3C2B,MAP3K7,PIK3CG,PIK3R1,NFATC2,IKBKE,PPP3CA
IL-12 Signaling and Production in Macrophages	0.048977882	0.187068214	PIK3C2B,AKT2,PIK3CG,PIK3R1,MAF,PRKCE,IKBKE,PRKCH,PRKCZ,PRKD1
Maturity Onset Diabetes of Young (MODY) Signaling	0.048977882	0.187068214	NEUROD1,CACNA1D,FOXA2

Supplementary Table 6: All HeLaS3 (exons 1-3) TCF7L2 Ingenuity Conical pathways with at least nominal $P < 0.05$

Supplementary Table 7: All HeLaS3 (exons 4-16) TCF7L2 Ingenuity Conical pathways with at least nominal $P<0.05$

Ingenuity Canonical Pathways	P-value	B-H Multipule testing correction p-value	Molecules
Aryl Hydrocarbon Receptor Signaling	0.00017	0.046	CDKN2A,NQO2,ALDH1L1,NFKB1,CCND1,SMARCA4,ARNT,NR2F1,TGM2,MYC,NCOA7,SP1,GSTM4,CHEK2,AHR,GSTA3,MED1,ALDH8A1,CDK6,SLC35A2,MDM2,FOS,CCND3,NFIB,NCOR2,ATR,GSTP1,CDK2,MGST3
Wnt/ β -catenin Signaling	0.00019	0.046	CDKN2A,FZD10,TGFBR3,CSNK1A1,BCL9,SOX13,CCND1,TCF7,SOX17,TGFBR2,MYC,SOX9,MAP3K7,SOX4,AXIN2,AKT2,CSNK1G3,CREBBP,MDM2,FZD9,TCF3,PPP2R2B,TLE4,CD4,4,TEL3,NR5A2,LEF1,DKK1,SFRP1,PPP2R5E,UBC,LRP1,TCF7L2,WNT5A
Type II Diabetes Mellitus Signaling	0.00035	0.050	SOCS1,SLC27A2,SOCS2,PKM,NFKB1,MAP3K7,SLC2A2,ACSL4,IRS2,NSMAF,TNFRSF11B,PPARG,PIK3C2B,AKT2,PIK3C2A,MAP3K1,CD36,IKBKE,CEBPB,ACSBG2,SLC2A4,IRS1,SH2B2,ENPP7,SOCS5
Cell Cycle: G1/S Checkpoint Regulation	0.00120	0.14	CDKN2A,HDAC4,HDAC8,SMAD3,CDK6,MDM2,CCND1,CDKN2B,SKP1/SKP1P2,MYC,NRG1,CCND3,MAX,ATR,CDK2
p53 Signaling	0.00191	0.16	CDKN2A,PIK3C2B,PIK3CA1,AKT2,GADD45B,TP63,JMY,PIK3C2A,MED1,MDM2,CCND1,SERpine2,BCL2,MDM4,SNAI2,SERPINB5,SFN,ATR,CHEK2,CDK2
Factors Promoting Cardiogenesis in Vertebrates	0.00204	0.16	SMAD2,FZD10,TGFBR3,FZD9,TCF7,NOG,ATF2,TGFBR2,NKX2-5,MAP3K7,MEF2C,LEF1,BMP7,DKK1,BMP6,LRP1,TCF7L2,CDK2
ILK Signaling	0.00347	0.21	FBLN1,HIF1A,NFKB1,CCND1,PDGFC,MYC,CFL2,RHOB,RHOD,IRS2,ITGB4,NOS2,ACTC1,ITGB1,PIK3C2B,AKT2,PIK3C2A,TMSB10/TMSB4X,CREBBP,ATF2,FOS,RND3,IRS1,SNAI2,SH2B2,PPP2R2B,LEF1,RP5K45,PTGS2,PPP2R5E,ITGB6,FNBP1
TR/RXR Activation	0.00380	0.21	PIK3C2B,AKT2,PIK3C2A,NXPH2,MED1,MDM2,THRA,PFK2,HIF1A,DIO3,SLC16A3,SCARB1,SREBF1,STRBP,NCOR2,TBL1XR1,THRB,PPARGC1A
Prolactin Signaling	0.00427	0.21	FYN,SOCS1,PIK3C2B,PIK3C2A,GRB2,SOCS2,CREBBP,CEBPB,NR3C1,TCF7,MYC,FOS,S1,IRS1,STAT1,SOCS5
Human Embryonic Stem Cell Pluripotency	0.00447	0.21	FZD10,FGF2,SMAD3,NGF,PDGFC,TCF7,NOG,TGFBR2,PIK3C2B,SMAD2,AKT2,PIK3C2A,S MAD7,SMAD6,FGFR2,FZD9,TCF3,INHBA,NTRK3,LEF1,BMP7,BMP6,TCF7L2,SALL4,WNT5A
ERK5 Signaling	0.00646	0.26	IL6ST,LIF,YWHAE,CREBBP,NGF,ATF2,MYC,YWHAQ,FOS,MAP3K8,MEF2C,RPS6KA5,SFN,ELK4
TGF- β Signaling	0.00676	0.26	SMAD2,GRB2,SMAD3,CREBBP,SKI,SMAD6,SMAD7,TGIF1,INHBA,BCL2,TGFBR2,NKX2-5,FOS,RUNX2,MAP3K7,BMP7,HNF4A
Molecular Mechanisms of Cancer	0.00724	0.26	CDKN2A,SMAD3,TAB2,CCND1,MYC,TGFBR2,CAMK2D,RHOB,ADCY9,SMAD2,PIK3C2B,A KT2,CREBBP,CDK6,FZD9,TCF3,MAX,CCND3,RND3,IRS1,LEF1,CFLAR,GNAL,FNBP1,CDK2,FZD10,FYN,PSEN2,HIF1A,NFKB1,CDKN2B,BCL2,RHOD,MAP3K7,BID,CHEK2,PMAIP1,PIK3C2A,GRB2,SMAD7,SMAD6,MDM2,FADD,GNAI3,FOS,BMP7,BMP6,ATR,LRP1,BCL2L11,WNT5A
Small Cell Lung Cancer Signaling	0.00794	0.27	MYC,PIK3C2B,AKT2,MAX,PIK3C2A,CKS1B,CDK6,BID,IKBKE,PTGS2,NFKB1,CDKN2B,CCN D1,CDK2,BCL2
Colorectal Cancer Metastasis Signaling	0.01000	0.30	IL6ST,SIAH1,FZD10,MMP20,SMAD3,MMP16,NFKB1,CCND1,PDGFC,TCF7,TGFBR2,MYC,GNG11,ARRB1,RHOB,RHOD,NOS2,STAT1,ADCY9,SMAD2,PIK3C2B,AKT2,PIK3C2A,GRB2,FZD9,IFNGR1,TCF3,TLR4,FOS,TLR5,RND3,LEF1,PTGS2,LRP1,FNBP1,TCF7L2,WNT5A
Protein Kinase A Signaling	0.01023	0.30	SMAD3,TCF7,TGFBR2,YWHAQ,ROCK2,PTPRC,CAMK2D,PDE7B,PPP3R1,CDKN3,ADCY9,YWHAE,CREBBP,PDE4B,PLCL2,TCF3,PTP4A1,ATF2,EPIM2A,MYL12A,DUSP1,PTPRS,LEF1,DUSP4,AKAP12,FLNB,PDIA3,PDE4A,PTP1B,CDC23,NFKB1,MPPE1,GNG11,PTPRJ,DU SP10,PTPN1,CNGB3,MTMR3,ATF1,MAP3K1,AKAP6,NFATC4,PDE4D,DUSP21,GNAI3,PPP1R14D,CDC14B,PDE5A,NFATC2,CNGB1,PTGS2,SFN,TCF7L2,AKAP1
L-glutamine Biosynthesis II (tRNA-dependent)	0.01175	0.31	QRSL1,PET112
PI3K Signaling in B Lymphocytes	0.01202	0.31	FYN,AKT2,ATF3,ATF1,PDIA3,IKBKE,PLCL2,NFATC4,NFKB1,ATF2,PTPRC,TLR4,FOS,CAM K2D,BCL10,VAV3,SYK,IRS1,PPP3R1,SH2B2,NFATC2,IRS2
Mouse Embryonic Stem Cell Pluripotency	0.01230	0.31	IL6ST,FZD10,PIK3C2B,AKT2,LEF1,PIK3C2A,GRB2,CREBBP,FZD9,TCF3,TCF7,LIFR,MYC,IDI1,MAP3K7,LEF1,TCF7L2,IDI4
Cell Cycle: G2/M DNA Damage Checkpoint Regulation	0.01445	0.34	YWHAQ,CDKN2A,MDM4,YWHAE,CKS1B,MDM2,SFN,ATR,SKP1/SKP1P2,CHEK2
FXR/RXR Activation	0.01698	0.34	PPARG,MLX1PL,AKT2,SLC4A2,LIPC,CYP27A1,CREBBP,IL33,ABC4,SCARB1,SREBF1,FO X2,FBP1,NR5A2,HNF4A,PPARGC1A
RhoGDI Signaling	0.01778	0.34	ARPC5,ROCK2,GNG11,CFL2,RHOB,RHOD,ARHGAP12,ACTC1,ITGB1,ITGA2,CREBBP,RD X,CDH6,ITGA3,CDH19,ARHGAP5,GNAI3,DGKZ,PIP5K1A,MYL12A,CDH9,RND3,CDH10,PP1R12B,CD44,CDH8,GNAL,FNBP1
Role of JAK2 in Hormone-like Cytokine Signaling	0.01778	0.34	SOCS1,IRS1,SH2B2,PTPN1,SOCS2,IRS2,STAT1,SOCS5
Stearate Biosynthesis I (Animals)	0.01778	0.34	SRD5A3,DHCR24,SLC27A2,ACSL4,ACOT9,ELOVL1,ACSBG2,HNF4A
Myc Mediated Apoptosis Signaling	0.01950	0.34	YWHAQ,CDKN2A,FADD,MYC,PIK3C2B,AKT2,YWHAE,PIK3C2A,GRB2,BID,SFN,BCL2
Urea Cycle	0.01950	0.34	ASS1,ARG2,CPS1
Thioredoxin Pathway	0.01950	0.34	TXNDC2,TXN,NXN
Thyroid Cancer Signaling	0.02455	0.39	PPARG,MYC,NTRK3,LEF1,NGF,TCF3,CCND1,TCF7,TCF7L2
NRF2-mediated Oxidative Stress Response	0.02512	0.39	FTL,NQO2,DNAJB2,SCARB1,MAP3K7,GSTM4,TXN,FKBP5,ACTC1,GSTA3,PIK3C2B,DNAJB8,PIK3C2A,MAP3K1,CREBBP,SLC35A2,JUNB,MAFK,BACH1,FOS,STIP1,CAT,DNAJC5B,AOX1,ENC1,ABC4,GSTP1,MGST3
Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis	0.02570	0.39	FZD10,TAB2,CSNK1A1,SP7,NFKB1,TCF7,BCL2,RUNX2,MAP3K7,PPP3R1,TNFRSF11B,ITGB1,PIK3C2B,AKT2,PIK3C2A,ITGA2,SMAD6,IKBKE,FZD9,NFATC4,ITGA3,TCF3,IL33,FATC2,BMP7,LEF1,DKK1,SFRP1,BMP6,LRP1,TCF7L2,WNT5A
Polyamine Regulation in Colon Cancer	0.02570	0.39	PPARG,MYC,MAX,AZIN1,SAT1,ODC1
LPS/IL-1 Mediated Inhibition of RXR Function	0.02818	0.42	LIPC,SLC27A2,CHST7,ALDH1L1,ABC41,MAOB,UST,SCARB1,MAP3K7,GSTM4,ACSL4,XPO1,CHST11,TNFRSF11B,GSTA3,ABC1,CYP2A7,MAP3K1,ALDH8A1,SLC35A2,ACSBG2,PAPSS2,SULT2B1,IL33,TLR4,SREBF1,CAT,NR5A2,ABC4,GSTP1,MGST3,PPARGC1A
Ephrin A Signaling	0.03020	0.43	ROCK2,EPHA7,FYN,PIK3C2B,CFL2,PIK3C2A,VAV3,EPHA5,EPHA2,EFNA1
PPAR Signaling	0.03090	0.43	PPARG,GRB2,MED1,CREBBP,IKBKE,NFKB1,PDGFC,IL33,NR2F1,FOS,MAP3K7,PTGS2,NCOR2,CITED2,PPARGC1A,TNFRSF11B

Chondroitin Sulfate Degradation (Metazoa)	0.03311	0.44	HYAL1,CD44,HEXB,HYAL4
Pancreatic Adenocarcinoma Signaling	0.03467	0.44	CDKN2A,SMAD2,PIK3C2B,AKT2,PIK3C2A,GRB2,SMAD3,MDM2,NFKB1,PDGFC,CCND1,C DKN2B,PLD1,BCL2,TGFBR2,PTGS2,STAT1,CDK2
Acute Myeloid Leukemia Signaling	0.03467	0.44	RUNX1,PIK3C2B,AKT2,PIK3C2A,GRB2,TCF3,NFKB1,CCND1,TCF7,MYC,KITLG,PIM1,LEF1 ,TCF7L2
Actin Nucleation by ARP-WASP Complex	0.03548	0.44	ROCK2,ITGB1,RND3,RHOB,GRB2,RHOD,ARPC5,ITGA2,PPP1R12B,ITGA3,FNBP1
Chronic Myeloid Leukemia Signaling	0.03715	0.44	CDKN2A,PIK3C2B,AKT2,HDAC4,HDAC8,PIK3C2A,GRB2,SMAD3,CDK6,MDM2,IKBKE,NFK B1,CCND1,MECOM,TGFBR2,MYC
Cardiomyocyte Differentiation via BMP Receptors	0.03802	0.44	NKX2-5,MAP3K7,SMAD6,BMP7,ATF2
Regulation of IL-2 Expression in Activated and Anergic T Lymphocytes	0.03890	0.44	SMAD2,FYN,GRB2,SMAD3,MAP3K1,IKBKE,NFATC4,NFKB1,TGFBR2,FOS,BCL10,PPP3R1, VAV3,NFATC2
HIF1α Signaling	0.03890	0.44	PIK3C2B,AKT2,MMP20,PIK3C2A,MAPK4,MMP16,CREBBP,MDM2,HIF1A,PDGFC,SLC2A4,S LC2A3,ARNT,EDN1,SLC2A2,EGLN3,NOS2
Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	0.03981	0.44	IL6ST,FZD10,SOCS1,FGF2,PDIA3,CSNK1A1,NFKB1,CCND1,PDGFC,TCF7,ROCK2,MYC,C AMK2D,MAP3K7,PPP3R1,NOS2,TNFRSF11B,PIK3C2B,IL8,AKT2,PIK3C2A,CREBBP,IKBKE ,FZD9,CEBPB,PLCL2,NFATC4,TCF3,ATF2,IL33,TLR4,FOS,TLR5,NFATC2,LEF1,DKK1,SFR P1,IRAK4,LRP1,TCF7L2,WNT5A
Role of IL-17A in Psoriasis	0.04365	0.46	S100A7,IL8,CCL20,CXCL5
Dermatan Sulfate Degradation (Metazoa)	0.04365	0.46	HYAL1,CD44,HEXB,HYAL4
CDK5 Signaling	0.04571	0.46	ITGB1,ADCY9,ITGA2,ITGA6,PPP1CB,ITGA3,NGF,CDK5R1,LAMC1,PPP1R14D,PPP2R2B,L AMB1,LAMA1,PPP2R5E,GNAL
GADD45 Signaling	0.04677	0.47	CCND3,GADD45B,CCND1,ATR,CDK2

Supplementary Table 8: All MCF7 TCF7L2 Ingenuity Conical pathways with at least nominal P<0.05

Ingenuity Canonical Pathways	P-value	B-H Mutipule testing correction p-value	Molecules
VDR/RXR Activation	5.37032E-07	0.000281838	SERPINB1,IL12A,CYP24A1,PDGFA,KLK6,HES1,PRKCZ,NCOA2,GADD45A,RUNX2,CSNK2A1,TGFBI2,CEBPA,PRKCE,NCOR1,SEMA3B,PRKD1,PRKCA,IFNG,LRP5,PPARD,MED1,IGFBP5,CEBPB,THBD,KLF4,SULT2A1,NCOA3,PRKC1,FOO1,IGFBP3,NCOA1,PRKCH,NCOR2,RXRA,S100G
Factors Promoting Cardiogenesis in Vertebrates	4.2658E-06	0.001122018	FZD10,NODAL,BMP4,AXIN1,ACVR2B,NOG,TCF7,PRKCZ,TGFBR2,MAP3K7,TGFBR2,PRKCE,GSK3B,ACVR1C,PRKD1,PRKCA,LRP5,ACVR1,FZD9,TCF7L1,TCF3,BMP5,ATF2,CCNE1,PRKCI,TGFBI3,MEF2C,LEF1,BMP7,PRKCH,DKK1,BMP6,LRP1,WNT11,ACVR2A,TCF7L2,CDK2
Wnt/ β -catenin Signaling	5.01187E-05	0.008709636	AXIN1,SOX12,CSNK1A1,TLE1,BCL9,WNT9A,SOX13,CCND1,TCF7,MYC,TGFBR2,SOX2,CSNK2A1,DKK2,GSK3B,SOX4,AKT2,AXIN2,APPL2,FZD9,TCF3,CDH1,CDH12,PPP2R3A,PPP2R2B,TGFBI3,LEF1,SPFRP1,FZD10,ACVR2B,SOX9,JUN,CDH3,MAP3K7,TGFBI2,AKT3,SOX14,ACVR1C,SOX5,LRP5,PPARD,CSNK1G3,WNT2B,GNAQ,ACVR1,TCF7L1,WNT3A,WNT10A,TLE4,CD44,DKK1,TCF7L2,LRP1,WNT11,ACVR2A,WNT5A
Human Embryonic Stem Cell Pluripotency	0.000104713	0.011220185	FZD10,NODAL,BMP4,KLK3,AXIN1,PDGFA,PIK3R1,SMAD3,WNT9A,NGF,TCF7,NOG,TGFBR2,SOX2,TGFBI2,PDGFR,AKT3,GSK3B,PIK3C2B,AKT2,PIK3C2A,WNT2B,ACVR1,SMAD7,SMAD6,PIK3C2G,FGFR2,FZD9,TCF7L1,TCF3,BMP5,INHBA,PDGFB,WNT3A,FOXO1,WNT10A,NTRK3,S1PR1,TGFBI3,LEF1,BMP7,BMP6,ZIC3,WNT11,TCF7L2,WNT5A,SALL4
Molecular Mechanisms of Cancer	0.000107152	0.011220185	SHH,BMP4,AXIN1,SUV39H1,PIK3R1,TAB2,ARHGEF1,KRAS,MAPK13,CCND1,PLCB1,GNA13,HIPIK2,PRKD1,FASLG,PIK3C2B,AKT2,TFDP1,PTCH1,TCF3,CDH1,CCND3,MAX,IRS1,ARHGEF6,GNA1,PSEN2,GNA14,PRKCZ,HHAT,JUN,BBC3,RHOU,BID,PRKCE,GRB2,RHOC,GNA12,GNAQ,PIK3C2G,FADD,FOS,CCNE1,RA,SGRP1,RASGRF1,RPB1,BMP7,BMP6,ATR,LRP1,GAB1,AKT1,DIRAS3,SMAD3,MYC,TGFBR2,E2F6,CAMK2D,GNAT1,RHOB,GSK3B,ADCY9,CDK6,FZD9,RA1B,P1,BCL2L1,CBL,RND3,ARHGEF16,MAPK10,TGFBI3,LEF1,PRKCH,CDK2,FZD10,ABL1,HIF1A,BCL2,RHOT1,MAP3K7,PRKAR1B,TGFBI2,AKT3,RHOB,PRKCA,LRP5,PIK3C2A,SMAD7,SMAD6,BMP5,XIAP,RHOV,PLCB4,PRKCI,FOXO1,PRKG2,BCL2L11,WNT5A,PRKAR1A
Heparan Sulfate Biosynthesis (Late Stages)	0.00030903	0.026915348	GAL3ST2,SULT1C4,HS2ST1,CHST12,GLCE,PRDX6,CHST15,SULT2A1,HS3ST3A1,SULT2B1,AACD,HS6ST1,HS3ST3B1,EXT2,UST,CHST11,HS6ST2,EXTL3,HS3ST1,HS6ST3,SULT1B1
Cholecystokinin/Gastrin-mediated Signaling	0.000457088	0.033884416	DIRAS3,KRAS,EPHA4,IL1F10,BCAR1,PRKCZ,ROCK2,JUN,RHOB,RHOT1,RHOU,PRKCE,PLCB1,GNA13,RHOF,PRKD1,PRKCA,RHOC,GRB2,ITPR2,GNA12,GNQA,Q,CKK,ITPR1,ATF2,ROCK1,FOS,RHOV,PLCB4,PRKCI,RND3,MEF2D,MAPK10,IL1B,MEF2C,PRKCH
Type II Diabetes Mellitus Signaling	0.000562341	0.037153523	SOCS1,PRKAB1,PRKAB2,SLC27A2,PIK3R1,PKM,SOCS2,PRKCZ,MAP3K7,SLC2A2,PIK3R2,PRKCE,AKT3,IRS2,SMPD3,PRKD1,PRKCA,TNFRSF11B,PPARG,PIK3C2B,AKT2,ACSL3,PIK3C2A,MAP3K1,CD63,PIK3C2G,IKBKE,CEBPB,ACSBG2,SLC2A4,PRKCI,IRS1,SH2B2,MAPK10,PRKG2,PRKCH,INSR,SOCS5,ACSL1
Aryl Hydrocarbon Receptor Signaling	0.000724436	0.042657952	HSPB3,ALDH4A1,GSTM5,IL6,CCND1,SMARCA4,ARNT,TGM2,NR2F1,MYC,JUN,TFI1,NCOA2,ALDH1A3,ALDH3A2,TGFBI2,GSTM4,NFE2L2,ALDH3A1,FASLG,AHR,GSTA3,TFDP1,MED1,CDK6,SLC35A2,NCOA3,CYP1B1,FOS,CCNE1,CCND3,NFIA,TGFBI2,HSP90AA1,IL1B,NFIB,NCOR2,DCT,NRIP1,RXRA,ATR,ESR1,GSTP1,CDK2
Glioblastoma Multiforme Signaling	0.000812831	0.042657952	FZD10,AXIN1,PDGFA,DIRAS3,PIK3R1,KRAS,WNT9A,CCND1,PTEN,MYC,E2F6,RHOB,RHOT1,RHOJ,IGF1R,PDGFR,AKT3,PLCB1,GSK3B,RHOF,PIK3C2B,AKT2,PIK3C2A,GRB2,ITPR2,RHOC,WNT2B,CDK6,PIK3C2G,PLCG1,FZD9,PLCL2,I,TPR1,TCF3,PDGFB,PLCZ1,RHOV,PLCB4,CCNE1,WNT3A,FOXO1,WNT10A,RND3,LEF1,WNT11,CDK2,WNT5A
Heparan Sulfate Biosynthesis	0.001	0.045708819	GAL3ST2,SULT1C4,XYLT1,HS2ST1,CHST12,GLCE,PRDX6,CHST15,SULT2A1,HS3ST3A1,SULT2B1,AACD,HS3ST3B1,HS6ST1,EXT2,UST,CHST11,HS6ST2,EXTL3,HS3ST1,HS6ST3,SULT1B1
Axonal Guidance Signaling	0.001047129	0.045708819	SHH,BMP4,PIK3R1,KRAS,NTN1,ADAMTS2,BAIAP2,PLCB1,GNA13,MYL10,PRKD1,ITGA4,PIK3C2B,AKT2,KALRN,PTCH1,PLCL2,SRGAP3,ARHGEF6,RTN4,EPHA2,GNAL,NRPI1,LRRK4C,UNC5A,SEMA6A,EPHA4,GNA14,PLXNA2,ABLIM1,PRKCZ,ACTR3,SRGAP1,PLXNA1,EFNA5,PFN2,PRKCE,RASSF5,UNC5C,ADAM2,PRP2,GRB2,GNA12,ITGA2,PIK3C2G,GNAQ,PLCG1,EPHA3,EFNA1,PLCZ1,SEMA3A,WNT3A,SEMA4D,NTRK3,ADAM10,BMP7,SEMA3C,BMP6,GNB2L1,LIMK2,WNT9A,ROCK2,GNAT1,SEMA3D,SDCBP1,PIK3R1,PIK3C2G,FARP2,EPHA7,FZD9,PDYPSL5,ADAMTS9,PDGFB,EPHA6,SDCBP,PRKCH,ERAP2,FZD10,ADAMTS7,PDGFA,TUBA3E,ABL1,NGF,BCAR1,ROBO1,EPHB6,GNG11,WASL,NFAT5,GLI3,PRKA1B,AKT3,SEMA3B,SHANK2,PRKCA,SEMA3D,PLXNC1,PIK3C2A,C9orf3,WNT2B,NFATC4,BMP5,EFNA4,ROCK1,PLCB4,PRKCI,WNT10A,TUBB6,LINGO1,PRKG2,NFATC2,EPHB3,SEMA4B,WNT11,PRKAR1A,WNT5A
Prolactin Signaling	0.001202264	0.047863009	PIK3C2B,SOCS1,PIK3C2A,GRB2,PRKCE,AKT3,SEMA4B,PRKCI,CEBPB,NR3C1,IRF1,PRKCZ,TCF7,MYC,FOS,PRKCI,JUN,IRS1,PRKCE,PRKCH,PRLR,STAT1,SOCS5,PRKD1,PRKCA
Small Cell Lung Cancer Signaling	0.001698244	0.064565423	PIK3R1,PAR6B,KRAS,CCND1,PRKCZ,PRKCE,AKT3,GSK3B,ITGB4,PRKD1,ITGB5,PRKCA,PIK3C2B,AKT2,PIK3C2A,GRB2,CDK6,PIK3C2G,PLCG1,AREG/ARL1,PIK3C2B,AKT2,TRAF3,PIK3C2A,TFDP1,PIK3R1,SUV39H1,PIK3C2G,CDK6,ABL1,IKBKE,CCND1,SKP2,BCL2,PTEN,MYC,BCL2L1,PIAS3,CCNE1,MAX,TRAF4,CKS1B,AKT3,BID,RXRA,CDK2
HER-2 Signaling in Breast Cancer	0.002344229	0.081283052	PIK3R1,PAR6B,KRAS,CCND1,PRKCZ,PRKCE,AKT3,GSK3B,ITGB4,PRKD1,ITGB5,PRKCA,PIK3C2B,AKT2,PIK3C2A,GRB2,CDK6,PIK3C2G,PLCG1,AREG/ARL1,PIK3C2B,AKT2,TRAF3,PIK3C2A,TFDP1,PIK3R1,SUV39H1,PIK3C2G,CDK6,ABL1,IKBKE,CCND1,PLCB1,GSK3B,PRKD1,ADCY9,PIK3C2B,AKT2,HDAC4,HDAC8,ITPR2,ITPR1,PLCL2,MAPK10,TGFBI3,RCAN3,PRKCH,SLC8A1,IL6ST,PRKZ,GNG11,MAP3K7,IGF1R,PRKAR1B,TGFBI2,ATF2,PRKCE,PRKCA,PIK3C2A,GRB2,MAP3K1,PIK3C2G,GNAQ,PLCG1,NFATC4,PLCZ1,CALM1 (includes others),PLCB4,PRKCI,MEF2D,PRKG2,MEF2C,PRKAR1A
Role of NFAT in Cardiac Hypertrophy	0.002570396	0.081283052	

Mouse Embryonic Stem Cell Pluripotency	0.002630268	0.081283052	IL6ST,FZD10,CD2,LIF,JAK1,BMP4,AXIN1,PIK3R1,KRAS,MAPK13,TCF7,MYC,LIFR,SOX2,CD1,MAP3K7,AKT3,GSK3B,PIK3C2B,AKT2,PIK3C2A,GRB2,PIK3C2G,FZD9,TCF7L1,TCF3,CD3,XIAP,WNT3A,LEF1,TCF7L2,CD4
PI3K Signaling in B Lymphocytes	0.003311311	0.097723722	BLNK,PIK3R1,ABL1,KRAS,PRKCZ,PTEN,PTPRC,NFAT5,JUN,CAMK2D,PPP3R1,AKT3,PLCB1,IRS2,VAV2,AKT2,ITPR2,PLCG1,IKBKE,ITPR1,NFATC4,PLCL2,ATF2,PLCZ1,CALM1 (includes others),FOS,PLCB4,PRKCI,CBL,CD180,DAPP1,BCL10,VAV3,SYK,IRS1,SH2B2,LYN,NFATC2,PLEKHA2
Ethanol Degradation IV	0.003630781	0.097723722	ALDH4A1,ACSL3,ACSS3,ALDH1A3,ALDH3A2,CAT,ACSS1,ALDH3A1,ACSL1,PRKAB1,PRKA2B,SMAD3,KRAS,IL6,ACVR2B,GNA14,ABC1,TFGB2,NR2F1,CHD5,JUN,MAP3K7,GPD2,TFGB2,PRKAR1B,PRKAA2,PLCB1,NCOR1,ACVR1C,ITGB5,PRKCA,ADCY9,GRB2,MED1,GNAQ,CD36,ACVR1,PLCG1,NR2C2,IKBKE,IL1R1,PLCL2,TGS1,NCOA3,PLCZ1,CAND1,PLCB4,IRS1,PRKAG2,TFGB3,IL1B,LYN,NFATC2,PLEKHA2
PPAR α /RXR α Activation	0.004265795	0.108893009	PRKAB1,PRKA2B,SMAD3,KRAS,IL6,ACVR2B,GNA14,ABC1,TFGB2,NR2F1,CHD5,JUN,MAP3K7,GPD2,TFGB2,PRKAR1B,PRKAA2,PLCB1,NCOR1,ACVR1C,ITGB5,PRKCA,ADCY9,GRB2,MED1,GNAQ,CD36,ACVR1,PLCG1,NR2C2,IKBKE,IL1R1,PLCL2,TGS1,NCOA3,PLCZ1,CAND1,PLCB4,IRS1,PRKAG2,TFGB3,IL1B,HSP90AA1,MF2C,NCOR2,INSR,RXRA,ACVR2A,PRKAR1A
Growth Hormone Signaling	0.004365158	0.108893009	PIK3C2B,SOCS1,PIK3C2A,PIK3R1,SOCS2,PIK3C2G,PLCG1,SLC2A4,ONECUT1,PRKCB,FOS,PRKCI,IRS1,CEBP α ,IGF1R,IGFBP3,PRKCE,PRKCH,RPS6KA2,S
G α q Signaling	0.004786301	0.108893009	TAT1,SOCS5,A2M,PRKDC1,PRKCA
Chondroitin Sulfate Degradation (Metazoa)	0.005128614	0.108893009	RGS18,DIRAS3,PIK3R1,GNB2L1,GNA14,CHRM3,AVPR1A,PRKCZ,ROCK2,GNG11,RHOB,RHOT1,PPP3R1,RHOU,PRKCE,AKT3,PLCB1,GSK3B,RHOF,PRKD1,A,VPR1B,PRKCA,ADCY9,GRB2,GN12,PIK3C2B,AKT2,PIK3C2A,ITPR2,RHOC,PIK3C2G,GNAQ,PLCG1,IKBKE,NFATC4,ITPR1,PLD1,ROCK1,CALM1 (includes others),RHOV,PLCB4,PRKCI,RND3,CALCR,NFATC2,PRKCH,AGTR1
Chondroitin Sulfate Biosynthesis (Late Stages)	0.005495409	0.108893009	HYAL1,CD44,HEXB,HEXA,SPAM1,ARSB,HYAL4
Oxidative Ethanol Degradation III	0.005754399	0.108893009	GAL3ST2,SULT1C4,HS2ST1,CHST12,CHST15,SULT2A1,HS3ST3A1,SLT2B1,HS3ST3B1,HS6ST1UST,CHST11,HS6ST2,HS3ST1,HS6ST3,SLT1B1
Methionine Degradation I (to Homocysteine)	0.005754399	0.108893009	ALDH4A1,ACSL3,ACSS3,ALDH1A3,ALDH3A2,ACSS1,ALDH3A1,ACSL1
Thrombin Signaling	0.00616595	0.108893009	SUV39H2,SUV39H1,PRMT8,FTSJ1,AHCYL2,MAT2A,EHMT1,AHCY,CAMK1D,DIRAS3,PIK3R1,GNB2L1,KRAS,ARHGEF1,MAPK13,GATA2,ROCK2,MYLK,CAMK2D,GNAT1,RHOB,PLCB1,GNA13,MYL10,PRKD1,ADCY9,PIK3C2B,A,KT2,ITPR2,ITPR1,PLCL2,RND3,ARHGEF16,ARHGEF6,PPP1R12B,PRKCH,GNA1,L,F2RL2,PPP1CB,GNA14,PRKCI,CNG11,RHOT1,RHOU,AKT3,PRKCE,GATA6,RHOF,PRKCA,PIK3C2B,GRB2,GN12,PIK3C2G,GNAQ,PLCG1,PLCZ1,R,OCK1,RHOV,PLCB4,PRKCI,GATA3
Dermatan Sulfate Biosynthesis (Late Stages)	0.006309573	0.108893009	GAL3ST2,SULT1C4,HS2ST1,CHST12,CHST15,SULT2A1,HS3ST3A1,SULT2B1,HS3ST3B1,HS6ST1UST,CHST11,HS6ST2,HS3ST1,HS6ST3,SLT1B1
Ephrin A Signaling	0.006309573	0.108893009	VAV2,EPHA7,PIK3C2B,PIK3C2A,PIK3R1,PIK3C2G,EPHA4,EPHA3,BCAR1,EFN4,EFNA1,ROCK1,ROCK2,EPHA6,VAV3,EFNA5,ADAM10,EPHA2
Renin-Angiotensin Signaling	0.006606934	0.108893009	PIK3R1,SHC3,KRAS,MAPK13,PRKCZ,JUN,PRKAR1B,PRKCE,STAT1,PRKD1,AGT,PRKCA,NOX1,ADCY9,PIK3C2B,PIK3C2A,GRB2,ITPR2,MAPK31,GNAQ,REN,PIK3C2G,PLCG1,ITPR1,ATF2,FOS,PRKCI,MAPK10,PRKAG2,PRKCH,PTGER2,AGTR1,AGTR2,PRKAR1A
TR/RXR Activation	0.006606934	0.108893009	NXPH2,TRH,PIK3R1,UCP1,HIF1A,DIO2,KLF9,NCOA2,SCARB1,AKT3,NCOR1,TBL1XR1,PIK3C2B,AKT2,PIK3C2A,ME1,PIK3C2G,PCK1,PFKP,DIO3,NCOA3,UCP3,SREBF1,ENO1,NCOA1,NCOR2,RXRA,THR8
Cell Cycle: G1/S Checkpoint Regulation	0.006606934	0.108893009	RBL2,HDAC4,HDAC8,ITDP1,SUV39H1,SMAD3,ABL1,CDK6,CCND1,SKP2,MYC,E2F6,CCNE1,CCND3,MAX,HDAC11,TFGB3,TFGB2,GSK3B,ATR,CDK2
p53 Signaling	0.007079458	0.112460497	JMY,GADD45G,PIK3R1,CCND1,BCL2,PTEN,JUN,GADD45A,STAG1,BBC3,AKT3,GSK3B,HIPK2,PIK3C2B,AKT2,TP63,PIK3C2A,TOPBP1,ME1,THBS1,PERP,PIK3C2G,PRPM,BCL2L1,KAT2B,MDM4,SNAI2,ATR,CDK2,DRAM1
Neuregulin Signaling	0.007943282	0.11939881	NRG2,BTC,PIK3R1,KRAS,PRKCZ,CDK5R1,TMEFF2,PTEN,MYC,ERBB4,PRKCE,AKT3,PRKD1,PRKCA,ITGA4,AKT2,GRB2,DCN,ITGA2,PLCG1,HBEFG,AREG/A,REGB,PRKCI,NRG3,TGF β ,HSP90AA1,PRKCH,EREG
Acetate Conversion to Acetyl-CoA	0.007943282	0.11939881	ACSL3,ACSS3,ACSS1,ACSL1
Glioma Signaling	0.008317638	0.1216186	CAMK1D,PDGFA,PIK3R1,UV39H1,ABL1,KRAS,CCND1,PRKCZ,PTEN,E2F6,CAMK2D,IGF1R,PDGFA,AKT3,PRKCE,PRKD1,PRKCA,PIK3C2B,AKT2,RBL2,PIK3C2A,TFDP1,GRB2,PIK3C2G,CDK6,PLCG1,PDGFB,CALM1 (includes others),PRKCI,PRKCH
Role of JAK2 in Hormone-like Cytokine Signaling	0.009120108	0.124738351	EP0,SOCS1,JAK1,PRL,IRS1,PTPN1,SH2B2,SOCS2,IRS2,PRLR,STAT1,SOCS5,SIRPA
Dermatan Sulfate Degradation (Metazoa)	0.009120108	0.124738351	IDS,HYAL1,CD44,HEXB,HEXA,SPAM1,HYAL4
Macropinocytosis Signaling	0.009332543	0.124738351	PIK3R1,ETS2,KRAS,IL6,CCND1,PRKCZ,ELF3,JUN,MAP3K7,HGF,PRKCE,AKT3,PRKD1,PRKCA,MAP3K9,PIK3C2B,AKT2,PIK3C2A,GRB2,MAP3K1,PIK3C2G,PLCG1,ATF2,ELF1,FOS,PRKCI,MAPK10,MAP3K8,PRKCH,ELF5,CDK2
HGF Signaling	0.01	0.12793813	HSPB3,DNAJC17,ASIC2,SGK1,PIK3R1,DNAJC12,ASIC3,HSPB8,KRAS,DNAJC15,SLC9A1,PRKCI,MAP3K9,PIK3C2B,AKT2,PIK3C2A,GRB2,MAP3K1,PIK3C2G,PLCG1,ATF2,ELF1,FOS,PRKCI,MAPK10,MAP3K8,PRKCH,ELF5,CDK2
Aldosterone Signaling in Epithelial Cells	0.010471285	0.12793813	SEPT9,PPP1CB,ARHGEF1,LIMK2,ROCK2,MYLK,ACTR3,PLXNA1,BAIAP2,IGF1R,PFN2,ARHGAP12,CDC42EP1,GNA13,MYL10,DLC1,ARHGAP6,NRP2,RTKN,GNAA12,RDX,CDCA42EP3,SEPT4,TTN,PLD1,ROCK1,KTN1,RHPN2,PIP5K1A,RAPG
RhoA Signaling	0.010471285	0.12793813	EF2,RND3,PPP1R12B,ARHGAP35,PIP4K2A,CDC42EP4
Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	0.010471285	0.12793813	SOCS1,TRAF3,AXIN1,PIK3R1,PRSS2,CSNK1A1,KRAS,IL6,WNT9A,CCND1,TCF7,ROCK2,MYC,CAMK2D,PPP3R1,TRAFA,PLCB1,DKK2,GSK3B,PRKD1,TNFRSF11B,PIK3C2B,AKT2,IL6R,FZD9,PLC2,TCF3,PDGFB,ATF2,PRKCH,LEF1,SFRP1,IL6ST,FZD10,PDGFA,IL1F10,PRKCZ,NFAT5,JUN,F2RL1,MAP3K7,CEBPA,PRKCE,AKT3,NOS2,PRKCA,LRP5,PIK3C2A,WNT2B,DAAM1,IL15,PIK3C2G,GNAQ,PLCG1,IKBKE,CEBPA,NFATC4,TCF7L1,IL1R1,PLC2,ROCK1,CALM1 (includes others),FOS,PLCB4,PRKCI,WNT3A,WNT10A,NFATC2,IL1B,DKK1,IRAK4,WNT11,LRP1,TCF7L2,RYK,WNT5A,IRAK2
Protein Kinase A Signaling	0.010715193	0.12793813	SHH,SMAD3,GNB2L1,TCF7,NTN1,PTEN,TGFBR2,MYLK,PTPRC,ROCK2,CAMK2D,RHO,PPP3R1,RYR3,PLCB1,GNA13,GSK3B,MYL10,EYA2,PRKD1,ADCY9,PTPRG,ITPR2,PTCH1,YWHAZ,PTPN3,ANAPC7,ITPR1,PLC2,TCF3,PTPDC1,TTN,ATF2,PDE8A,AKAP13,EPM2A,TGF β 3,PTPRS,PRKCH,LEF1,DUSP4,PTPRA,SIRPA,PTPN21,AKAP12,FLNB,ANAPC1/ANAPC1P1,PTPN13,PPP1R3C,DUSP6,PT

			PN14,PDE4A,PPP1CB,CDC23,PRKCZ,PHKA2,AKAP11,MPP1,PPMPE1,DUSP5,GNG11,HHAT,NFAT5,GLI3,DUSP10,PTPN1,PRKAR1B,TGFB2,PRKCE,CNGB3,PRKCA,MTMR3,PTPRK,MAP3K1,GNAQ,PLCG1,AKAP6,TCF7L1,NFATC4,PDE4D,ROCK1,PLCZ1,CALM1 (includes others),AKAP2/PALM2-,AKAP2,PLCB4,PRKCI,CDC14B,PRKAG2,NFATC2,PDE8B,PTPRR,EYA1,PTPRT,TCF7L2,DUSP16,PRKAR1A
G Beta Gamma Signaling	0.011220185	0.128824955	GNB2L1,KRAS,GNA14,PRKCZ,GNG11,GNAT1,PRKAR1B,PRKCE,AKT3,GNA13,CAV2,CAV3,PRKCZ,PRKCA,AKT2,GRB2,GNA12,GNAQ,PLCG1,HBEGF,KCNJ3,PRKCI,ARHGEF6,PRKAG2,PRKCH,KCNJ6,GNAL,PRKAR1A
Thyroid Cancer Signaling	0.012022644	0.134276496	PPARG,KLK3,GDNF,KRAS,TCF7L1,NGF,TCF3,CCND1,TCF7,MYC,CDH1,NTRK3,LEF1,RXRA,TCF7L2
Transcriptional Regulatory Network in Embryonic Stem Cells	0.012022644	0.134276496	LHX5,TRIM24,CDX2,MEIS1,TCF7L1,HOXB1,SET,FOXC1,ONECUT1,SOX2,CDY,L,GATA6,SKIL,ZIC3,ZFHX3
ErbB Signaling	0.012882496	0.135831345	NRG2,BTC,PIK3R1,KRAS,MAPK13,PRKCZ,JUN,ERBB4,PRKCE,GSK3B,PRKD1,PRKCA,PIK3C2B,PIK3C2A,GRB2,PIK3C2G,PLCG1,HBEGF,AREG/AREGB,FOS,PRKCI,FOXO1,NRG3,TGFA,MAPK10,PRKCH,EREG
Xenobiotic Metabolism Signaling	0.013182567	0.135831345	LIPC,CAMK1D,PIK3R1,MAF,GCLC,KRAS,IL6,MAPK13,CHST15,ARNT,HS6ST1,MAOB,CAMK2D,NR1I2,ALDH3A2,CHST11,HS6ST3,HS3ST1,ALDH3A1,AHR,PRKD1,MAP3K9,PIK3C2B,HDAC4,ME1,GRIP1,MDK1,SULT2A1,HS3ST3B1,PP2R2A,PP2R2B,NCOA1,HSP90AA1,PRKCH,RXRA,GSTP1,ALDH4A1,GAL3ST2,SULT1C4,GSTM5,HS2ST1,FM05,HS3ST3A1,PRKCZ,UST,MAP3K7,ALDH1A3,GSTM4,PRKCE,HS6ST2,SMOX,NOS2,NEF2L2,CITED2,PRKCA,GSTA3,PIK3C2A,MAP3K1,PIK3C2G,CHST12,CYP1B1,ESL,SULT2B1,PRKCI,CAT,IL1B,MAP3K8,NCOR2,NRIP1,DNAJC7,SULT1B1
Cardiac Hypertrophy Signaling	0.013182567	0.135831345	DIRAS3,PIK3R1,GNB2L1,KRAS,MAPK13,IL6,TGFBR2,ROCK2,RHOB,GNAT1,PP3R1,PLCB1,GSK3B,GNA13,MYL10,ADCY9,PIK3C2B,MAP3K9,IL6R,PLCL2,A,TF2,RND3,IRS1,TGFB3,MAPK10,GNAL,EIF2B4,GNA14,JUN,GNG11,RHOT1,MAP3K7,TGFB2,IGF1R,PRKAR1B,RHOU,RHOF,ADRB2,CACNA1D,PIK3C2A,MAPKAP3,RHOC,GRB2,GNA12,MAP3K1,GNAQ,PIK3C2G,PLCG1,HBEGF,AREG,PLCZ1,ROCK1,CALM1 (includes others),RHOV,PLCB4,MEF2D,PRKAG2,MEF2C,MAP3K8,ADRA2C,PRKAR1A,SOC5S1,JAK1,PIK3R1,SOC5S2,KRAS,PRKCZ,JUN,PRKAR1B,IGF1R,CSNK2A1,A,KT3,IRS2,PIK3C2B,AKT2,PIK3C2A,GRB2,PIK3C2G,YWHAZ,IGFBP3,IGFBP2,F,OS,NEDD4,PRKCI,NOV,FOXO1,IRS1,IGFBP3,PRKAG2,SOCS5,PRKAR1A
IGF-1 Signaling	0.013489629	0.135831345	GAB2,PIK3C2B,PIK3C2A,GRB2,PIK3R1,PIK3C2G,PLCG1,KRAS,PRKCZ,MYC,F,OS,JUN,PRKCI,PRKCE,IRS2,PRKCH,STAT1,PRKD1,PRKCA
Thrombopoietin Signaling	0.013489629	0.135831345	MMP20,JAK1,AXIN1,MMP16,DIRAS3,PIK3R1,SMAD3,GNB2L1,KRAS,IL6,WNT9A,CCND1,TCF7,TGFBR2,MYC,RHOB,GSK3B,ADCY9,PIK3C2B,AKT2,ADRBK2,I,L6R,FZD9,TCF3,BCL2L1,CDH1,RND3,TGFB3,MAPK10,LEF1,PTGER2,IL6ST,FZD10,JUN,GNG11,ARRB1,RHOT1,TGFB2,PRKAR1B,RHOU,AKT3,STAT1,RHOF,NOS2,MMP17,IFNG,LRP5,PIK3C2A,GRB2,RHOC,WNT2B,PIK3C2G,TCF7L1,FO,S,RHOU,WNT3A,WNT10A,PRKAG2,TCF7L2,LRP1,WNT11,PRKAR1A,WNT5A
Colorectal Cancer Metastasis Signaling	0.013803843	0.135831345	SUV39H2,SUV39H1,PRMT8,FTSJ1,AHCYL2,MAT2A,EHMT1,AHCY
Cysteine Biosynthesis III (mammalia)	0.014454398	0.139636836	GAL3ST2,SULT1C4,XYLT1,CHSY1,HS2ST1,CHST12,CHST15,CHST1,CHST15,SUL2T1A1,HS3ST3A1,SULT2B1,HS6ST1,HS3ST3B1,UST,CHST11,HS6ST2,HS3ST1,HS6ST3,SUL1T1B1
Chondroitin Sulfate Biosynthesis	0.015848932	0.148593564	RHOC,GRB2,GNA12,DIRAS3,ITGA2,KRAS,ROCK2,ROCK1,RHOU,ACTR3,WAS
Actin Nucleation by ARP-WASP Complex	0.016595869	0.154525444	L,RND3,RHOB,RHOT1,BAI2AP2,PPP1R12B,RHOU,RHOF,ITGA4,PIK3R1,DIRAS3,GNB2L1,KRAS,GNA14,BCAR1,PRKCZ,ROCK2,JUN,GNG11,G,NAT1,RHOB,RHOT1,RHOU,AKT3,PRKCE,PLCB1,GNA13,RHOU,ADCY9,MLY10,PRKD1,PRKCA,ADCY9,PIK3C2B,AKT2,PIK3C2A,ITPR2,RHOC,GNA12,PIK3C2G,GNAQ,ITPR1,ROCK1,FOS,RHOU,PLCB4,PRKCI,RND3,MAPK10,LYN,PRKCH,ELMO1,GNAL
CXCR4 Signaling	0.016982437	0.155238701	ALDH4A1,MAOB,ALDH1A3,ALDH3A2,COMT,SMOX,ALDH3A1,LRTOMT,SULT1B1
Dopamine Degradation	0.019498446	0.174180687	TRIM24,RDH10,PIK3R1,SMAD3,NR2F2,MAPK13,PRKCZ,SMARCA4,PTEN,NR2F1,JUN,ALDH1A3,RDH16,TGFB2,PRKAR1B,CSNK2A1,PRKCE,AKT3,NCOR1,N,TC5C1B,CITED2,PRKD1,PRKCA,ADCY9,AKT2,RDH14,MED1,MAP3K1,SMAD7,S,MAP6,KAT2B,FOS,PRKCI,TAFF4,SMARCA2,CRABP2,MAPK10,IGFBP3,NCOA1,TGFB3,PRKAG2,PRKCH,NRIP1,RXRA,CARM1,PRKAR1A
RAR Activation	0.019952623	0.176603782	GAB2,SUV39H1,SMAD3,PIK3R1,ABL1,KRAS,CCND1,TGFB2,MYC,E2F6,HDA C11,CTBP2,TGFB2,AKT3,PIK3C2B,AKT2,BRL2,B,HDAC4,HDAC8,TFDP1,PIK3C2A,GRB2,CDK6,PIK3C2G,IKBKE,MECOM,BCL2L1,TGFB3
Chronic Myeloid Leukemia Signaling	0.020417379	0.178648757	GAL3ST2,SULT1C4,XYLT1,CHSY1,HS2ST1,CHST12,CHST15,SUL2T1A1,HS3ST3A1,SULT2B1,HS6ST1,HS3ST3B1,UST,CHST11,HS6ST2,HS3ST1,HS6ST3,SUL1T1B1
Dermatan Sulfate Biosynthesis	0.023442288	0.198152703	IL6ST,FZD10,LIF,JAK1,BMP4,AXIN1,PIK3R1,KRAS,WNT9A,SOX2,LIFR,AKT3,G,AT6A,GSK3B,PIK3C2B,AKT2,PIK3C2A,GRB2,WNT2B,CDX2,PIK3C2G,FZD9,TC F7L1,BMP5,WNT3A,WNT10A,BMP7,BMP6,WNT11,SALL4,WNT5A,TCL1A
Role of NANOG in Mammalian Embryonic Stem Cell Pluripotency	0.023442288	0.198152703	SHH,FZD10,BMP4,AXIN1,PTCH1,WNT2B,ZFD9,TCF7L1,WNT9A,TCF3,BMP5,T,CF7,WNT3A,GLI3,WNT10A,LEF1,BMP7,GSK3B,BMP6,WNT11,TCF7L2,WNT5A
Basal Cell Carcinoma Signaling	0.02630268	0.215774441	VAV2,CD3E,GRB2,SMAD3,MAP3K1,PLCG1,TOB1,IKBKE,KRAS,NFATC4,TGFB R2,CALM1 (includes others),FOS,JUN,NFAT5,BCL10,VAV3,PPP1R1,ZAP70,MAPK10,TGFB3,TGFB2,NFATC2,CARD11
Regulation of IL-2 Expression in Activated and Anergic T Lymphocytes	0.026915348	0.217770977	IL12A,PIK3R1,MAF,CLU,MAPK13,PRKCZ,PON1,JUN,TGFB2,PRKCE,AKT3,SER PINA1,NOS2,STAT1,PRKD1,PRKCA,PPARG,IFNG,PIK3C2B,AKT2,PIK3C2A,RA B7A,PIK3C2G,IKBKE,CEBPB,IRF1,STAT4,FOS,PRKCI,IL12B,MAPK10,NCOA1,T GFB3,MAP3K8,PRKCH,IRF8,RXRA
IL-12 Signaling and Production in Macrophages	0.028840315	0.229614865	JAK1,POLR2A,PRKAB2,PRKAB1,CD3E,SGK1,PIK3R1,SMAD3,PBX1,KRAS,IL6,MAPK13,TAF13,TSC22D3,PGR,TGFB2,RHSP4,HMGB1,PPP3R1,PIK3C2B,AK T2,MED1,PKC1,NCOA1,BCL2L1,KAT2B,TAFF4,SMARCA2,TGFB3,NCOA1,MAPK 10,HSP90AA1,ESR1,PRL,NR3C1,SMARCA4,BCL2,JUN,NFAT5,NCOA2,MAP3K 7,TGFB2,CEBPB,PRKAA2,AKT3,NCO1,FKBP5,NOS2,STAT1,AGT,ADRB2,IFN G,PIK3C2A,GRB2,MAP3K1,PIK3C2G,IKBKE,NFATC4,CEBPB,TSG101,FOS,PR KAG2,NFATC2,IL1B,NCO2,NRIP1,A2M
Glucocorticoid Receptor Signaling	0.029512092	0.234422882	PIK3C2B,SOCS1,AKT2,JAK1,PIK3C2A,GRB2,PIK3R1,SOCS2,PIAS1,GNAQ,PIK 3C2G,KRAS,IL6,STAT4,PIAS3,BCL2L1,FOS,PTPN1,AKT3,STAT1,SOCS5
JAK/Stat Signaling	0.030199517	0.234422882	NODAL,BMP4,GRB2,SMAD3,SMAD6,ACVR1,SMAD7,KRAS,ACVR2B,MAPK13,I NHBB,INHBB,TGIF1,SMURF1,BCL2,TGFB2,FOS,JUN,RUNX2,MAP3K7,TGFB3
TGF-β Signaling	0.030902954	0.23659197	,TGFB2,BMP7,ACVR1C,ACVR2A

Antiproliferative Role of TOB in T Cell Signaling	0.031622777	0.23659197	PABPC1,TGFBR2,CCNE1,SMAD3,TGFB3,TGFB2,TOB1,TWSG1,CDK2,SKP2,BMP4,AXIN1,PIK3R1,TAB2,CSNK1A1,IL6,WNT9A,TCF7,RUNX2,PPP3R1,DKK2,GSK3B,TNFRSF11B,PIK3C2B,AKT2,TFD9,TCF3,CBL,MAPK10,LEF1,SFRP1,FZD10,IL1F10,BCL2,SMURF1,JUN,NFAT5,MAP3K7,AKT3,IFNG,LRP5,PIK3C2A,WNT2B,ITGA2,SMAD6,PIK3C2G,IKBKE,TCF7L1,NFATC4,IL1R1,BMP5,XIAP,CALM1 (includes others),FOS,WNT3A,FOXO1,WNT10A,CALCR,NFATC2,IL1B,BMP7,DKK1,BMP6,TCF7L2,LRP1,WNT11,WNT5A
Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis	0.031622777	0.23659197	PIK3C2B,AKT2,JAK1,PIK3C2A,GRB2,ITPR2,PIK3R1,MAP3K1,PIK3C2G,PLCG1,ITPR1,MAPK13,FOS,JUN,CSNK2A1,AKT3,STAT1,PRKCA
EGF Signaling	0.033884416	0.240990543	GRIN2B,GRM2,SLC1A4,GRID2,GLS,SLC1A3,SLC38A1,GRIP1,GRINA,GRM7,C ALM1 (includes others),GNG11,GRK4,GRID4,GLUL,SLC1A2,GRK2,GRK1
Glutamate Receptor Signaling	0.033884416	0.240990543	ALDH4A1,MAOB,ALDH1A3,ALDH3A2,SAT1,SMOX,ALDH3A1
Putrescine Degradation III	0.033884416	0.240990543	ALDH4A1,ACSL3,ACSS3,RDH14,DHRS2,ALDH1A3,ALDH3A2,ACSS1,ALDH3A1
Ethanol Degradation II	0.035481339	0.244906324	ACSL1,DHRS4
GDNF Family Ligand-Receptor Interactions	0.035481339	0.244906324	DOK5,PIK3C2B,PIK3C2A,GFNA,ARTN,GRB2,ITPR2,GFRA3,PIK3R1,PIK3C2G,P LCG1,KRAS,ITPR1,FOS,JUN,IRS1,GFRA1,MAPK10,IRS2,DOK1,FRS2
LPS/IL-1 Mediated Inhibition of RXR Function	0.038904514	0.26915348	LIPC,SLC27A2,CHST15,ABC1A,ABC9,HS6ST1,MAOB,CYP2A13/CYP2A6,SCA RB1,NR112,ALDH3A2,CHST11,XPO1,HS6ST3,HS3ST1,FABP7,ALDH3A1,TNFR SF11B,ACSL3,SULT2A1,HS3ST3B1,NCOA1,RXRA,ACOX3,ABC4,GSTP1,ALD H4A1,GAL3ST2,SULT1C4,SLC10A1,GSTM5,HS2ST1,IL1F10,FM05,HS3ST3A1, JUN,UST,ALDH1A3,MAP3K7,GSTM4,HS6ST2,SMOX,GSTA3,CYP2A7,MAP3K1, SLC35A2,IL1R1,CHST12,ACSBG2,SULT2B1,SREBF1,CAT,IL1B,SULT1B1,ACSL 1
RhoGDI Signaling	0.040738028	0.271643927	DIRAS3,GNB2L1,ARHGEF1,LIMK2,GNA14,CDH11,ROCK2,GNG11,ACTR3,WAS L,GNAAT1,RHOB,CDH3,RHOT1,RHOU,ARHGAP12,GNA13,RHOF,MYL10,DLC1,I TG4,PRKCA,ARHGAP6,RHOC,GNA12,ITGA2,RDX,CDH6,GNQ,CDH18,GRIP 1,ROCK1,DGKZ,PIP5K1A,RHOV,CDH1,CDH12,RND3,ARHGEF16,ARHGEF6,C D44,PPP1R12B,ARHGAP35,PIP4K2A,ESR1,GNAL
Non-Small Cell Lung Cancer Signaling	0.040738028	0.271643927	PIK3C2B,AKT2,PIK3C2A,TFDP1,GRB2,ITPR2,SUV39H1,PIK3R1,ABL1,PIK3C2G CDK6,PLCG1,KRAS,ITPR1,CND1,TGFA,AKT3,RASSF5,RXRA,PRKCA
p70S6K Signaling	0.042657952	0.278612117	F2RL2,JAK1,PIK3R1,KRAS,PRKCZ,F2RL1,PLCB1,AKT3,PRKCE,EEF2K,PRKD1 ,PRKCA,AGT,PIK3C2B,AKT2,PIK3C2A,GRB2,GNQ,YWHAZ,PIK3C2G,PLCG1 ,PLCL2,PLD1,PLCZ1,PLCZ4,PRKCI,PPP2R3A,SYK,IRS1,PPP2R2B,LYN,PRKCH ,AGTR1
UDP-D-xylene and UDP-D-glucuronate Biosynthesis	0.043651583	0.282487997	UXS1,UDGDH
L-DOPA Degradation	0.043651583	0.282487997	COMT,LRTOMT
Ovarian Cancer Signaling	0.044668359	0.282487997	FZD10,AXIN1,PIK3R1,SUV39H1,ABL1,KRAS,WNT9A,CCND1,TCF7,BCL2,PTEN ,ARRB1,EDN1,PRKAR1B,PMS2,AKT3,GSK3B,PIK3C2B,AKT2,PIK3C2A,TFDP1 ,FGF9,WNT2B,PIK3C2G,FZD9,TCF7L1,TCF3,WNT3A,WNT10A,CD44,PRKAG2,L EF1,WNT11,TCF7L2,PRKAR1A,WNT5A
CREB Signaling in Neurons	0.044668359	0.282487997	GRM2,PLR2D,PIK3R1,GRID2,GNB2L1,KRAS,GNA14,PRKCZ,GNG11,CAMK2 D,GRID1,GNAAT1,PRKAR1B,AKT3,PRKCE,PLCB1,GNA13,GRK2,PRKD1,GRK1 ,PRKCA,ADCV9,PIK3C2B,GRIN2B,AKT2,PIK3C2A,GRB2,ITPR2,GNA12,PIK3C2 G,GNQ,PLCG1,PLCL2,ITPR1,ATF2,PLCZ1,GRM7,CALM1 (includes others),PLCB4,PRKCI,GRK4,PRKAG2,PRKCH,GNAL,PRKAR1A
Estrogen-Dependent Breast Cancer Signaling	0.046773514	0.28840315	PIK3C2B,HSD17B3,AKT2,HSD17B13,PIK3C2A,PIK3R1,TERT,PIK3C2G,KRAS,C CND1,ATF2,FOS,JUN,CYP19A1,IGF1R,AKT3,HSID17B12,AKR1C4,ESR1
Pyridoxal 5'-phosphate Salvage Pathway	0.046773514	0.28840315	MAP3K9,DAPK1,AKT2,SGK1,CSNK1A1,CDK6,LIMK2,PRKX,NEK2,PDXK,PIM1 ,PRPF4B,PRKA2,PRKCE,MAP3K8,PRKCH,ACVR2A,CDK2,DYRK1A
Docosahexaenoic Acid (DHA) Signaling	0.050118723	0.299916252	BCL2L1,PIK3C2B,AKT2,FOXO1,PIK3C2A,PIK3R1,PIK3C2G,IL1B,BID,AKT3,GSK 3B,BCL2,APP

Supplementary Table 9: All PANC1 TCF7L2 Ingenuity Conical pathways with at least nominal $P < 0.05$

Ingenuity Canonical Pathways	P-value	B-H Multipole testing correction p-value	Molecules
Molecular Mechanisms of Cancer	4.89779E-06	0.002691535	RAP2B,RAF1,SHH,RAPGEF1,BMP4,AXIN1,PIK3R1,TAB2,CDKN2C,KRAS,GSK3A,RBL1,CCND1,HIPK2,FASLG,PRKD1,SMAD2,PIK3C2B,CCNE2,AKT2,CREBBP,PTCH1,NFKB2,TCF3,CDH1,MAX,IRS1,ARHGEF6,CFLAR,ARHGEF9,GNAL,CAMK2G,MAP2K6,RAP1B,RAP2A,LRP6,BMPR2,PSEN2,MAP3K5,PRKCZ,CHEK1,HHAT,JUN,BBC3,SOS1,RHOH,BID,PRKCE,ARHGEF3,CASP8,PK2,GRB2,GNAA12,MDM2,BAK1,SIN3A,PRKCG,FADD,FOS,GNAI3,CCNE1,RASGRF1,RBPJ,BMP7,BMP6,ATR,CASP7,LRP1,CTNNB1,BIRC2,GAB2,JAK1,SMAD3,MYC,TGFBR2,PTK2,CTNNB2,CAMK2D,RHOB,GNAT1,MRS,FDZ2,BIRC3,E2F2,ADCY9,CYCS,CDK6,FZD9,APC,PIK3R3,BCL2L1,BMPR1B,CBL,RND3,ARHGEF16,GNAA1,TGFBR3,FZD5,LEF1,FNBP1,RELA,BMP2,ABL1,HIF1A,NFKB1,RHOH,BCL2,NFKBIA,MAP3K7,RHOT1,TGFBR2,RHOH,PAK4,LRP5,ARHGEF12,PIK3C2A,GNAA1,SMAD7,SMAD6,BMP5,XIAP,GNAA12,FZD8,MAPK14,PRKCI,FOXO1,N1,PRKAG2,PIK3CB,BCL2L11
Factors Promoting Cardiogenesis in Vertebrates	1.25893E-05	0.003467369	BMP4,MYL2,AXIN1,TGFBR3,BMP2,LRP6,BMPR2,NOG,TCF7,PRKCE,TGFBR2,MAP3K7,TGFBR2,PRKCE,FZD2,ACVR1C,PRKD1,SMAD2,LRP5,CCNE1,FZD9,TCF3,BMP5,ACVR1B,APC,PRKCG,ATF2,FZD8,BMPR1B,CCNE1,MAPK14,PRKCI,TGFBR3,FZD5,LEF1,MEF2C,BMP7,DKK1,BMP6,GATA4,WNT11,LRP1,TCF7L2
Wnt/ β -catenin Signaling	2.29087E-05	0.004265795	CSNK1G1,AXIN1,TGFBR3,SOX12,CSNK1A1,WNT16,GSK3A,BCL9,CCND1,TCF7,SOX2,MYC,TGFBR2,RARA,PPM1L,CSNK2A1,FZD2,SOX4,AKT2,AXIN2,CREBBP,CSNK1D,FZD9,TCF3,ACVR1B,APC,CDH2,CDH12,GNAA1,PP2R2B,TGFBR3,TLE3,LEF1,SOX8,FZD5,DVL2,SFRP1,MMMP7,SFRP2,LRP6,BMPR2,SOX9,JUN,MAP3K7,DKK3,CDH3,TGFBR2,SOX14,PPP2R2C,ACVR1C,UBB,LRP5,PPARD,CSNK1G3,WNT2B,HDAC1,MDM2,FZD8,WNT10A,SOX6,TLE4,CD44,NR5A2,BTRC,DKK1,PPP2R5E,UBC,WNT11,LRP1,TCF7L2
Prolactin Signaling	6.60693E-05	0.009120108	SOCS3,RAF1,SOCS1,PRL,PIK3R1,SOCS6,SOS2,PDPK1,KRAS,GNR3C1,TCF7,PRK CZ,MYC,JUN,SP1,SOS1,MRS,PRKCE,STAT1,STAT5,PRKD1,STA5A,PIK3C2B,PIK3C2A,GRB2,CREBBP,PLCG1,CEBPB,STAT3,PRKCG,PIK3R3,POS,PRKCI,IRS1,PIK3CB,SOCS5
mTOR Signaling	0.000169824	0.015135612	PRKAB2,PRKAB1,PIK3R1,PDPK1,EIF4A2,KRAS,RPS7,VEGFA,RPS24,RHOB,EIF3B,EIF4G2,PPM1L,MRS,PRKD1,PIK3C2B,AKT2,RHEB,DDIT4,EIF4G3,VEGFC,EIF3E,PLD1,PIK3R3,ATG13,RPS6KA6,RND3,IRS1,PPP2R2B,RPS15,PPS6KA1,FNBP1,EIF3K,NAPEPLD,FKBP1A,RPS13,HIF1A,PRR5,L,PDGFC,RHOH,PRKCE,RPS27,MTOR,RHOT1,RPS9,RPS16,PRKAA2,EIF3A,RPTOR,RHOH,PRKCE,RPS20,PPP2R2C,RHOH,GNB1L,RPS3,EIF3H,PIK3C2A,EIF3F,RPS19,PRKCG,RPS12,PRKCI,RPS10,RPS5,RPS26,PRKG2,PRR5,PPS6KA4,PIK3C2B,PPP2R5E,UBC
Signaling by Rho Family GTPases	0.000194984	0.015135612	RAF1,MAP3K11,MYL2,SEPT9,PIK3R1,DIAPH3,GNB2L1,PIKFYVE,CLIP1,ROCK2,GNB1,MYLK,PTK2,MAP3K10,STMN1,CFL2,GNAT1,RHOB,E2R,BAIAP2,MRS,ARPC1A,ACTG2,MYL10,ACTR2,PIK3C2B,MAP3K9,CFL1,SEPT7,RDX,CDH18,WASF1,NFKB2,PLD1,PIK3R3,CDH2,MYL12A,PIP5K1A,CDH1,CDH12,RND3,MYL12B,ARHGEF16,ARHGEF6,GNAA1,PPP1R12B,CDH8,GNB2,ARHGEF9,FNBP1,GNAL,RELAA1,RHOH,PRKCE,CDH11,CDH11,CDH7,JUN,WASL,GNG11,CDH3,RHOT1,CIT,RHOH,ARHGEF3,GNB1L,RHOH,ITGB1,PAK4,PAK2,ARHGEF12,PIK3C2A,GNAA12,ACTB,ITGA2,GNAA1,CDH6,VIM,ITGA3,GNNG5,GNAA12,GNAA13,PRKCI,PIK3CB,CD42EP4
PEDF Signaling	0.000213796	0.015135612	RAF1,RELA,GDNF,BDNF,PIK3R1,KRAS,NGF,NFKB1,TCF7,BCL2,TCF12,ROCK2,IKBKG,NFKBIA,SOD2,MRS,CASP8,FASLG,PPARG,PIK3C2B,AKT2,PIK3C2B,WASF1,CFLAR,CASP7
Hypoxia Signaling in the Cardiovascular System	0.000218776	0.015135612	EPO,UBE2H,UBE2A,UBE2D2,HIF1A,CREB5,ARNT,UBE2F,PTEN,VEGFA,HS90B1,NFKBIA,UN,HSP90AB1,UBE2B,EDN1,UBE2V1,COP55,CREBBP,UBE2R2,CREB3,CSNK1D,BIRC6,MDM2,UBE2S,SLC2A4,ATF2,HSP90AA1,UBE2E1,LDAH,UBE2I
Huntington's Disease Signaling	0.000288403	0.017782794	VT11A,SGK1,PIK3R1,GNB2L1,PDPK1,HSPA5,CREB5,CDK5R1,GNB1,MAP3K10,HSPA4,VAMP3,TCERG1,POLR2H,PRKD1,PIK3C2B,AKT2,HDAC4,HDAC2,HDAC8,CYCS,CLTC,CREB3,CREBBP,TBP,DNM3,ITPR1,UBE2S,STX1A,RPH3A,NAFP,ATF2,HDAC5,HSPA8,PIK3R3,DYNC112,BCL2L1,HTGNB2,CAPN2,POLR2I,BDNF,NGF,PRKCE,ZNG2,TGM2,MTOR,JUN,GNG11,SP1,SO1,IGF1R,PRKCE,NCOR1,DNAJB1,GNB1L,CASP8,BET1L,EGFR,NEUROD1,HDAC9,GRIN2B,UBB,PIK3C2A,YKT6,GRB2,GLS,HDAC1,HIP1,HSPA2,SNAP25,GNG5,SIN3A,PRKCG,CASP12,PRKCI,CAPNS1,HAP1,PIK3CB,NCOR2,UGC,GOSR2,CASP7
Thrombin Signaling	0.000446684	0.020417379	RAF1,MPPR15,MYL2,PIK3R1,GNB2L1,PDPK1,KRAS,PLCH2,GATA2,ROCK2,GNB1,MYLK,PTK2,PLCD3,PLCE1,CAMK2D,GNAT1,RHOB,MRS,MYL10,PRKD1,ADCY9,PIK3C2B,AKT2,ITPR2,TBP,ITPR1,NFKB2,PIK3R3,MYL12A,RND3,MYL12B,ARHGEF16,GNAA1,ARHGEF6,GNB2,PPP1R12B,ARHGEF9,GNAL,FNBP1,CAMK2G,RELA,F2R2,GNAT5,PDIA3,NFKB1,RHOH,GNG7,PRKCE,GNG11,RHOT1,SOS1,RHOH,PRKCE,ARHGEF3,RHOH,GNB1L,EGFR,ARHGEF12,PIK3C2A,GRB2,GNAA12,GNAA1,PLCG1,GNG5,PRKCG,GNAA12,GNAA13,MAPK14,PRKCI,PIK3CB,GATA3,GATA4
ILK Signaling	0.000446684	0.020417379	MYL2,PIK3R1,PDPK1,GSK3A,CREB5,CCND1,PTEN,MYC,NCK2,PTK2,VEGFA,CFL2,RHOB,PPM1L,IRS2,ACTG2,ITGB4,ITGB5,PIK3C2B,AKT2,CFL1,FERMT2,CREB3,CREBBP,VEGFC,NFKB2,ATF2,PIK3R3,CDH1,RND3,IRS1,ARHGEF6,PPP2R2B,MYH3,RSU1,LEF1,ACTN4,ITGB6,FNBP1,MAP2K6,RELA,FLNB,BMP2,ITGB8,HIF1A,MYH11,NFKB1,RHOH,PDGFC,MTOR,JUN,RHOT1,PPAP2B,RHOH,PPP2R2C,RHOH,NOS2,NACA,MUC1,ITGB1,PXN,PIK3C2A,ACTB,VIM,FOS,LIMS1,SH2B2,MYH9,PIK3CB,PPS6KA4,PPP2R5E
EIF2 Signaling	0.000457088	0.020417379	RAF1,RPL22,RPL27A,EIF1,PIK3R1,PDPK1,EIF4A2,KRAS,EIF2A2,RPS7,RPS24,EIF3B,EIF4G2,EIF1AX,PAIP1,EIF5,MRS,PLR12,PLP8,EIF2AK1,PIK3C2B,AKT2,RPL3,RPL27,RPL37,EIF4G3,RPL23A,EIF3E,RPLP0,PIK3R3,RPL15,RP

		L10,RPS15,RPS15A,RPL13A,RPLP1,EIF3K,RPL31,EIF2B4,RPL22L1,RPS13,RPL37A,RPS27,RPS9,SOS1,RPS16,RPL35,RPLP2,EIF3A,RPS20,RPS3,EIF3H,PIK3C2A,EIF3F,RPL34,GRB2,RPL17,RPS19,EIF2C2,RPL21,RPS12,RPS10,RPS5,RPS26,RPL36A,PIK3CB,EIF2AK3,RPS14
Growth Hormone Signaling	0.000489779	0.020417379
Role of JAK2 in Hormone-like Cytokine Signaling	0.00060256	0.021877616
Axonal Guidance Signaling	0.000616595	0.021877616
PI3K Signaling in B Lymphocytes	0.000630957	0.021877616
Chronic Myeloid Leukemia Signaling	0.000776247	0.024547089
Ephrin Receptor Signaling	0.000794328	0.024547089
Type II Diabetes Mellitus Signaling	0.000933254	0.026915348
Small Cell Lung Cancer Signaling	0.001230269	0.033113112
IGF-1 Signaling	0.001318257	0.033113112
ERK5 Signaling	0.001348963	0.033113112
RhoGDI Signaling	0.001380384	0.033113112
Integrin Signaling	0.001479108	0.033884416
TNFR1 Signaling	0.001513561	0.033884416
Erythropoietin Signaling	0.001949845	0.040738028
PPAR Signaling	0.001995262	0.040738028
ATM Signaling	0.002187762	0.041686938
HER-2 Signaling in Breast Cancer	0.002187762	0.041686938
Estrogen-Dependent Breast	0.002290868	0.042657952

Cancer Signaling			3,CREBPP,TERT,KRAS,NFKB2,CREB5,NFKB1,CCND1,ATF2,PIK3R3,FOS,J UN,SP1,MRAS,IGF1R,HSD17B12,PIK3CB,STAT5B,HSD17B2,EGFR
Cardiac Hypertrophy Signaling	0.002398833	0.042657952	RAF1,MAP3K11,MYL2,PIK3R1,GNB2L1,HAND1,KRAS,IL6,PLCH2,TGFB2, GNB1,ROCK2,PLCD3,MAP3K10,PLCE1,GNAT1,RHOB,MRAS,MYL10,ADRA 1B,ADCY9,MAP3K9,PIK3C2B,CREBPP,IL6R,ATF2,PIK3R3,MYL12A,RND3,M YL12B,IRS1,GNAO1,TGFB3,GNB2,RPS6KA1,GNAL,FNBP1,HSPB1,MAP2K6 ,EIF2B4,PDIA3,ATF6,MAP3K5,RHOH,GNG7,MTOR,GNG11,ADR1B,JUN,RH OT1,MAP3K7,SOS1,IGF1R,RHOU,TGFB2,RHOF,GNB1L,ADR2B,CACNA1D, MEF2BNB- MEF2B,PIK3C2A,GRB2,GNA12,MAP3K1,CHP1,GNA11,MEF2A,PLCG1,NFAT C4,GNG5,GNAI2,GNAI3,CALM1 (includes others),MAPK14,PRKAG2,ADR2C,PIK3CB,MAP3K8,MEF2C,GATA4
Germ Cell-Sertoli Cell Junction Signaling	0.002511886	0.042657952	MAP3K11,AXIN1,PIK3R1,MLT4,PDPK1,KRAS,TGFB2,PTK2,MAP3K10,CT NNA2,RHOB,MRAS,TUBA1C,MTMP2,ACTG2,JUP,PIK3C2B,MAP3K9,ITGA6, GSN,TUBA1B,PIK3R3,CDH2,CDH1,RND3,TGFB3,ACTN4,FNBP1,MAP2K6,T UBA3E,MAP3K5,BCAR1,RHOH,WASL,SORBS1,RHOT1,MAP3K7,PPAP2B,T GFB2,RHOU,RHOF,RABBB,ITGB1,EPN1,PXN,PAK4,PAK2,PIK3C2A,TJP1,A CTB,MAP3K1,ITGA2,ITGA3,MAPK14,TUBA1A,MAP3K8,PIK3CB,A2M,CTNN D1
Regulation of eIF4 and p70S6K Signaling	0.002570396	0.043651583	RAF1,EIF1,PIK3R1,PDPK1,EIF4A2,KRAS,PAIP2,EIF2A,RPS7,RPS24,EIF3B, EIF4G2,EIF1AX,PPM1,PAIP1,MRAS,PIK3C2B,AKT2,EIF4G3,EIF3E,PIK3R3, IRS1,PPP2R2B,RPS15,PPM1A,EIF3K,EIF2B4,RPS13,PRKCZ,MTOR,RPS27 ,RPS9,RPS16,SOS1,EIF3A,RPS20,PPP2R2C,RPS3,ITGB1,PIK3C2A,EIF3H, EIF3F,GRB2,ITGA2,RPS19,EIF2C2,ITGA3,RPS12,RPS10,MAPK14,RPS5,RP S26,PIK3CB,PPP2R5E,RPS14
PI3K/AKT Signaling	0.002691535	0.043651583	GAB2,RAF1,RELA,JAK1,PIK3R1,GDF15,PDPK1,KRAS,GSK3A,MAP3K5,NFK B1,CCND1,PRKCZ,PTEN,BCL2,YWHAQ,IKBKG,MTOR,HSP90B1,NFKBIA,H SP90AB1,FOXO3,SOS1,PPM1,LMRAS,PPP2R2C,THEM4,ITGB1,RHEB,AKT 2,GRB2,ITGA2,YWHAZ,MDM2,IKBKE,NFKB2,ITGA3,SYNJ2,PIK3R3,BCL2L1, FOXO1,LIM3,PPP2R2B,HSP90AA1,PIK3CB,MAP3K9,PPP2R5E,SFN
Acute Myeloid Leukemia Signaling	0.002884032	0.043651583	MAP2K6,RUNX1,RAF1,RELA,PIK3R1,KRAS,NFKB1,CCND1,TCF7,MYC,MTO R,PIM1,RARA,SOS1,MRAS,CEBPJA,JUP,STAT5B,STAT5A,PIK3C2B,AKT2,PI K3C2A,GRB2,NFKB2,STAT3,TCF3,PIK3R3,KITLG,PIK3CB,LEF1,MAP2K5,TC F7L2,PIM2
Prostate Cancer Signaling	0.002951209	0.043651583	RAF1,RELA,PIK3R1,ABL1,PDPK1,KRAS,CREB5,NFKB1,CCND1,PTEN,BCL2 ,HSP90B1,MTOR,NFKBIA,HSP90AB1,SOS1,MRAS,PIK3C2B,CCNE2,AKT2,P IK3C2A,GRB2,CREBPP,CREB3,MDM2,NFKB2,SIN3A,ATF2,PIK3R3,CCNE1, FO XO1,HSP90AA1,PIK3CB,LEF1
Cardiomyocyte Differentiation via BMP Receptors	0.003019952	0.043651583	BMPR1B,BMP4,MYL2,MAP3K7,BMP2,SMAD6,BMPR2,BMP7,BMP5,GATA4, ATF2
TGF-β Signaling	0.003019952	0.043651583	MAP2K6,RAF1,BMP4,SMAD3,BMP2,SKI,BMPR2,KRAS,HOXC9,TGIF1,BCL2, TGFB2,JUN,RUNX2,MAP3K7,SOS1,TGFB2,MRAS,SERpine1,ACVR1C,SM AD2,GRB2,CREBPP,HDAC1,SMAD7,SMAD6,ACVR1B,INHBB,INHBA,FOS,B MPR1B,MAPK14,TGFB3,SMURF2,BMP7
Mouse Embryonic Stem Cell Pluripotency	0.003162278	0.045708819	IL6ST,RAF1,ID2,JAK1,BMP4,LIF,T,AXIN1,PIK3R1,BMPR2,KRAS,TGF7,MYC, LIFR,SOX2,ID1,MAP3K7,SOS1,MRAS,FZD2,PIK3C2B,AKT2,PXN,PIK3C2A,GRB2, CREBPP,FZD9,STAT3,TCF3,XIAP,APC,PIK3R3,FZD8,MAPK14,PIK3CB,FZD 5,LEF1,DVL2,TCF7L2,ID4
Thrombopoietin Signaling	0.003467369	0.047863009	RAF1,GAB2,PIK3R1,KRAS,PRKCZ,MYC,JUN,SOS1,MRAS,PRKCE,IRS2,ST AT1,STAT5B,PRKD1,PIK3C2B,STAT5A,PIK3C2A,GRB2,PLCG1,STAT3,PRK CG,PIK3R3,FOS,PRKCI,PIK3CB
HGF Signaling	0.003981072	0.05370318	RAP1B,RAF1,RAPGEF1,MAP3K11,PIK3R1,ETS2,KRAS,MAP3K5,IL6,CCND1 ,PRKCZ,PTK2,ELF4,MAP3K10,JUN,ELF3,MAP3K7,HGF,SOS1,MRAS,PRKC E,PRKD1,ETS1,MAP3K9,PIK3C2B,AKT2,PXN,PIK3C2A,GRB2,MAP2K1,PLC G1,STAT3,PRKCG,ATF2,MET,PIK3R3,FOS,PRKCI,PIK3CB,MAP3K8
IL-9 Signaling	0.004570882	0.060255959	STAT5A,RELA,SOCS3,PIK3C2B,JAK1,PIK3C2A,PIK3R1,SOCS2,STAT3,NFK B2,NFKB1,PIK3R3,IRS1,PIK3CB,IRS2,STAT5B,STAT1
Apoptosis Signaling	0.004786301	0.0616595	RAF1,ADAM17,PIK3R1,PDPK1,KRAS,PRKCZ,CDK5R1,TMEFF2,PTEN,MYC, HSP90B1,MTOR,HSP90AB1,ERBB4,SOS1,GRB2,MRAS,PRKCE,ERRF1,ST AT5B,PRKD1,EGFR,ITGB1,STAT5A,AKT2,GRB2,ITGA2,PLCG1,ITGA3,PRK CG,AREG/AREGB,PIK3R3,PICK1,PRKCI,HSP90AA1
Neuregulin Signaling	0.005888437	0.072443596	MAP2K6,RAF1,RELA,MAP2K11,PIK3R1,TAB2,MAP3K5,NFKB1,MAP3K10,IK BKG,JUN,NFKBIA,MAP3K7,BIRC3,MAP3K9,PIK3C2B,AKT2,PIK3C2A,MITF,C HP1,MAP3K1,IKBKE,NFKB2,GSN,XIAP,PIK3R3,CALM1 (includes others),FOS,TRAF2,MAPK14,CBL,NFATC2,MAP3K8,PIK3CB,BIRC2
RANK Signaling in Osteoclasts	0.005888437	0.072443596	FLN,AP2A1,PIK3R1,ABL1,KRAS,ITGB8,PRKCZ,CD55,CAV1,MRAS,PRKCE ,ITGB4,ACTG2,PRKD1,ITGB1,PIK3C2B,AP2B1,PIK3C2A,ACTB,CLTC, ITGA2,ITGA6,PLCG1,ITGA3,AP2S1,PRKCG,PIK3R3,PRKCI,CLTA,CLTCL1,T FRC,ITGA1,PIK3CB,ITGB6,CXADR
Virus Entry via Endocytic Pathways	0.006025596	0.072443596	SOX2,HOXB5,ISL1,T,MESP1,GATA4,SP4
Embryonic Stem Cell Differentiation into Cardiac Lineages	0.006456542	0.075857758	RELA,MAP3K11,JAK1,TWF1,IL15,NFKB2,IL6,NFKB1,FRK,PRKCZ,PTK2,PRK CG,PLTK7,STAT1
IL-15 Production	0.006606934	0.075857758	RAF1,LIP,PIK3R1,GNB2L1,CSNK1A1,HAND1,KRAS,IL6,PLCH2,TGFB2,GN B1,PLCD3,PLCE1,CAMK2D,MRAS,PRKD1,ADCY9,PIK3C2B,AKT2,HDAC4,H DAC2,HDAC8,ITPR2,ITPR1,HDAC5,PIK3R3,TGFB3,GNB2,RCAN3,CAMK2G, IL6ST,MAP2K6,PDIA3,PRKCZ,GNG7,GNG11,MAP3K7,SOS1,TGFB2,IGF1R, PRKCE,GNB1L,HDAC9,PIK3C2A,MEF2BNB- MEF2B,GRB2,MAP3K1,CHP1,HDAC1,MEF2A,GNA11,PLCG1,NFATC4,GNG5 ,PRKCG,GNAI2,CALM1 (includes others),GNAI3,MAPK14,PRKCI,PRKAG2,MEF2C,PIK3CB,GATA4
Role of NFAT in Cardiac Hypertrophy	0.00691831	0.075857758	RAF1,RAPEF1,PIK3R1,KRAS,HIF1A,ARNT,VEGFA,JUN,HGF,SOS1,MRAS, EGLN3,ETS1,PIK3C2B,UBB,PAK4,AKT2,PAK2,PIK3C2A,SLC2A1,GRB2,CRE BBP,PDGFB,PIK3R3,MET,FOS,CUL2,PIK3CB,UBC
Renal Cell Carcinoma Signaling	0.00691831	0.075857758	GADD45B,JMY,GADD45G,PIK3R1,RRM2,CCND1,BCL2,PTEN,CHEK1,JUN, GADD45A,STAG1,BBC3,CCNK,HIPK2,W1,PIK3C2B,AKT2,TP63,PIK3C2A,T OPBP1,MED1,HDAC1,CSNK1D,PERP,PRPMP,MDM2,TP53BP2,PIK3R3,BCL2
p53 Signaling	0.007413102	0.079432823	

			L1,PCNA,MDM4,MAPK14,PIK3CB,SNF,ATR,DRAM1
Death Receptor Signaling	0.008128305	0.085113804	RELA,TNFSF10,MAP4K4,MAP3K5,NFKB1,BCL2,TANK,IKBKG,NFKBIA,CRA DD,BID,CASP8,BIRC3,FASLG,TNFRSF21,CYCS,IKBKE,NFKB2,XIAP,FADD, TRAF2,CFLAR,CASP7,BIRC2,HSPB1
PTEN Signaling	0.008317638	0.085113804	MAST2,RAF1,RELA,PIK3R1,TGFB3,BMPR2,PDPK1,KRAS,GSK3A,NFKB1, BCAR1,CCND1,PRKCZ,PTEN,BCL2,TGFB3,PTK2,FGFR3,IKBKG,FOXO3,S OS1,CSNK2A1,IGF1R,MRAS,FASLG,EGFR,ITGB1,AKT2,GRB2,ITGA2,FGFR 2,IKBKE,NFKB2,CNKS3,FOXG1,ITGA3,SYNJ2,PIK3R3,BCL2L1,BMPR1B,C BL,FOXO1,PIK3CB,MAGI2,BCL2L1
Hereditary Breast Cancer Signaling	0.00851138	0.085113804	GADD45B,GADD45G,PIK3R1,KRAS,DD2,CCND1,RAD50,SMARCA4,PTEN, CHEK1,GADD45A,MRAS,SLC19A1,POLR2H,BLM,PIK3C2B,HDAC9,UBB,AK T2,HDAC4,C17orf70,HDAC8,PIK3C2A,HDAC2,WEE1,HDAC1,CREBBP,CDK6 .FANCC,FANCL,CDK1,HDAC5,PIK3R3,MSH2,H2AFX,C19orf40,MSH6,PIK3C B,UBC,SFN,POLR2I,HLTF,ATR
TWEAK Signaling	0.00851138	0.085113804	RELA,TRAF3,CYCS,IKBKE,NFKB2,NFKB1,XIAP,FADD,TRAF2,IKBKG,NFKB1 A,BID,CASP8,BIRC3,CASP7,BIRC2
JAK/Stat Signaling	0.008709636	0.085113804	SOC53,RAF1,SOCS1,JAK1,PIK3R1,SOCS6,PIAS1,SOCS2,KRAS,IL6,MTOR, SOS1,PTPN1,MRAS,STAT5B,STAT1,PIK3C2B,STAT5A,AKT2,PIK3C2A,GRB 2,STAT3,STAT4,PIK3R3,POS,BCL2L1,PIK3C2B,SOCS5
NF- κ B Activation by Viruses	0.008912509	0.085113804	RAF1,RELA,PIK3R1,KRAS,NFKB1,PRKCZ,IKBKG,NFKBIA,ITGAV,MRAS,PR KCE,PRKD1,ITGB5,ITGB1,PIK3C2B,AKT2,PIK3C2A,ITGA2,MAP3K1,ITGA6,T BP,IKBKE,NFKB2,ITGA3,PRKCG,PIK3R3,TRAF2,PRKCI,PIK3CB,ITGA1
Human Embryonic Stem Cell Pluripotency	0.009120108	0.087096359	BMP4,AXIN1,PIK3R1,SMAD3,WNT16,PDPK1,GSK3A,TCF7,TGFB2,FGFR3, SOX2,MRAS,FZD2,PIK3C2B,SMAD2,AKT2,FGFR2,FZD9,TCF3,APC,PDGFB, INHBA,PIK3R3,BMPR1B,TGFB3,LEF1,FZD5,IL6ST,RELA,SFRP2,IL1F10,NFKB1,P FC,NOG,TGFBI2,PIK3C2A,WNT2B,SMAD7,SMAD6,BMP5,FZD8,FOXO1,WNT 10A,S1PR1,PIK3CB,BMP7,BMP6,TCF7L2,ZIC3,WNT11,SALL4
Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	0.009549926	0.089125094	SOC53,RAF1,AXIN1,PIK3R1,KRAS,IL6,CREB5,PLCH2,CCND1,VEGFA,TRA F4,PRKD1,PIK3C2B,AKT2,CREBBP,STAT3,TCF3,ATF2,SFRP1,CAM K2G,MAP2K6,PDIA3,LRP6,PRKCZ,JUN,CCL2,F2RL1,CEBPA,PRKCE,IL15,P LCG1,PRKCG,FOS,CALM1 (includes others),TRAF2,CSF1,TCF7L2,LRP1,IRAK4,IRAK2,RYK,SOCS3,TRAF3,MMP3 ,CSNK1A1,WNT16,TCF7,CEBPG,MYC,ROCK2,PLCD3,IKBKG,PLCE1,TRAF3 IP2,CAMK2D,MRAS,FZD2,TNFRSF11B,IL8,MIF,IL6R,VEGFC,CD9,PDGFB, APC,PIK3R3,IL18,GNAO1,LEF1,FZD5,IL6ST,RELA,SFRP2,IL1F10,NFKB1,P DGFC,IRAK1,NFAT5,NFKBIA,DKK3,MAP3K7,NOS2,LRP5,PIK3C2A,WNT2B, CHP1,IKBKE,CEBPB,NFATC4,FZD8,PRKCI,MAPK14,WNT10A,NFATC2,PIK3 CB,DKK1,WNT11
TNFR2 Signaling	0.009772372	0.091201084	TANK,FOS,RELA,IKBKG,TRAF2,JUN,NFKBIA,MAP3K1,IKBKE,NFKB2,NFKB 1,BIRC3,XIAP,BIRC2
Actin Nucleation by ARP-WASP Complex	0.01	0.091201084	ITGB1,ACTR2,GRB2,GNA12,ITGA2,WASF1,KRAS,ITGA3,RHOH,ROCK2,NC K2, WASL,RND3,RHOB,RHOT1,SOS1,BAIAP2,MRAS,PPP1R12B,RHOU,ARP C1A,RHOF,FNPB1,VASP
Role of Oct4 in Mammalian Embryonic Stem Cell Pluripotency	0.011481536	0.1	NR6A1,KDM5B,FOXA1,NR2F2,CDX2,MEF2A,SH3GLB1,HOXB1,IGF2BP1,PA NR4A1,SOX1,SOX2,AQR,CCNF,FOXA1,RAFA,NR5A2,NR5A1,PHB,SALL4
IL-8 Signaling	0.011481536	0.1	RAF1,MYL2,PIK3R1,GNB2L1,CXCL1,KRAS,MAP4K4,CCND1,GNB1,PTK2,V EGFA,ROCK2,IKBKG,RHOB,ITGA2,MRAS,ITGB5,PRKD1,IL8,PIK3C2B,AKT2 .VEGFC,MMP2,PLD1,PIK3R3,BCL2L1,CDH1,RND3,MYL12B,GNB2,FNB1P,1,R ELA,NAPEPLD,NFKB1,PDGFC,RHOH,PRKCZ,GNG7,IRAK1,BCL2,MTOR,JU N,GNG11,RHOT1,RHOH,PRKCE,GNB1L,RHOH,VASP,LASP1,EGFR,PAK2,P IK3C2A,GNA12,GNA11,IKBKE,GNG5,PRKCG,GNA12,GNA13,FOS,PRKCI,PIK 3CB,IRAK4,IRAK2
Glioblastoma Multiforme Signaling	0.011748976	0.1	RAF1,AXIN1,PIK3R1,NF2,WNT16,KRAS,PLCH2,CCND1,PTEN,MYC,PLCD3, PLCE1,RHOB,MRAS,FZD2,E2F2,PIK3C2B,AKT2,ITPR2,CDK2,FZD9,ITPR1,T CF3,PDGFB,APC,PIK3R3,IGF2,RND3,LEF1,FZD5,FNPB1,PDIA3,PDGFC,RH OH,MTOR,RHOT1,SOS1,IGF1R,RHOH,RHOF,EGFR,PIK3C2A,GRB2,WNT2 B,PLCG1,MDM2,FZD8,CNE1,NF1,WNT10A,FOXO1,PIK3CB,WNT11
PPAR α /RXR α Activation	0.011748976	0.1	PPARA,RAF1,PRKAB1,PRKAB1,SMAD3,TGFB3,KRAS,MAP4K4,IL6,PLCH2 .ABC1,MRAS,PLCE1,MRAS,ITGB5,ADCY9,SMAD2,ME1,CREBBP,NFKB2,NOCA3,ACVR1B,IRS1,TGFB3,HSP90AA1, MAP2K6,RELA,PDIA3,BMPR2,NFKB1,HSP90B1,NFKBIA,JUN,CHD5,HSP90 AB1,MAP3K7,FASN,SOS1,TGFB2,PRKAA2,NCOR1,GOT2,STAT5B,ACVR1C .GRB2,ACOX1,CD36,CKAP5,PLCG1,IKBKE,TGS1,MAPK14,PRKAG2,MEF2C .NCOR2
NRF2-mediated Oxidative Stress Response	0.012302688	0.101391139	RAF1,PIK3R1,GCLC,KRAS,DNAJC15,SOD2,SCARB1,ABCC1,MRAS,FOSL1, DNAJA2,MRAS,PLCE1,MRAS,ITGB5,ADCY9,SMAD2,ME1,CREBBP,NFKB2,NOCA3, DNAJC16,PRKCI,PIK3C2B,AKT2,ITPR2,CDK2,FZD9,ITPR1,T CF3,APC,PIK3R3,BCL2L1,CDH1,RND3,TGFB3,GNB2,LEF1,FZD5,FNPB1,SIA H1,IL6ST,RELA,MMP7,LRP6,NFKB1,RHOH,PDGFC,GNG7,GNG11,JUN,ARR B1,RHOT1,SOS1,RHOH,TGFB2,RHOH,STAT1,GNB1L,NOS2,PTGER4,MMP1 7,EGFR,LRP5,PIK3C2A,GRB2,WNT2B,GNG5,FZD8,FOS,WNT10A,MSH2,MS H6,PRKAG2,PIK3CB,WNT11,LRP1,TCF7L2
CD27 Signaling in Lymphocytes	0.012302688	0.101391139	MAP2K6,RELA,MAP3K9,MAP3K11,CYCS,MAP3K1,IKBKE,NFKB2,MAP3K5,N FKB1,BCL2L1,FOS,MAP3K10,TRAF2,IKBKG,JUN,NFKBIA,MAP3K7,BID,MAP 3K8,CASP8,MAP2K5
Colorectal Cancer Metastasis Signaling	0.012589254	0.101391139	MMP20,JAK1,ADRBK1,MMP3,AXIN1,SMAD3,MMP16,PIK3R1,GNB2L1,WNT 16,KRAS,IL6,CCND1,TCF7,VEGFA,GNB1,TGFB3,MYC,RHOB,MRAS,FZD2, ADCY9,SMAD2,PIK3C2B,AKT2,IL6R,VEGFC,FZD9,MMP2,NFKB2,STAT3,TC F3,APC,PIK3R3,BCL2L1,CDH1,RND3,TGFB3,GNB2,LEF1,FZD5,FNPB1,SIA H1,IL6ST,RELA,MMP7,LRP6,NFKB1,RHOH,PDGFC,GNG7,GNG11,JUN,ARR B1,RHOT1,SOS1,RHOH,TGFB2,RHOH,STAT1,GNB1L,NOS2,PTGER4,MMP1 7,EGFR,LRP5,PIK3C2A,GRB2,WNT2B,GNG5,FZD8,FOS,WNT10A,MSH2,MS H6,PRKAG2,PIK3CB,WNT11,LRP1,TCF7L2
Aryl Hydrocarbon Receptor Signaling	0.012589254	0.101391139	ALDH4A1,RELA,NQO2,IL6,NFKB1,CCND1,SMARCA4,CHEK1,ARNT,TGM2, MYC,NR2F1,HSP90B1,NCOA7,JUN,HSP90AB1,SP1,NR0B2,ALDH1A3,RARA .TGFB2,NFE2L2,FASLG,AHR,GSTA3,CCNE2,MED1,GSTA4,TYR,CDK6,SLC 35A2,MDM2,NFKB2,CYP1B1,GSTO1,NCOA3,FOS,CCNE1,ALDH1L2,NFIA,T GFB3,HSP90AA1,NFIB,ALDH1A1,NRIP1,NCOR2,ATR,MGST3,HSPB1
Telomerase Signaling	0.013182567	0.103038612	RAF1,PIK3R1,TERT,ABL1,ETS2,PDPK1,KRAS,MYC,ELF4,HSP90B1,ELF3,H SP90AB1,PPM1L,SOS1,MRAS,PPP2R2C,PO1,EGFR,ETS1,HDAC9,PI K3C2B,AKT2,HDAC4,HDAC2,PIK3C2A,HDAC8,GRB2,HDAC1,HDAC5,PIK3R 3,TERF2,PPP2R2B,HSP90AA1,PIK3CB,TINF2,PPP2R5E

Role of PKR in Interferon Induction and Antiviral Response	0.013803843	0.106414302	MAP2K6,RELA,TRAF3,CYCS,TAB2,IKBKE,NFKB2,NFKB1,ATF2,FADD,TRAF2,IKBKG,MAPK14,NFKBIA,MAP3K7,BID,CASP8,STAT1
Transcriptional Regulatory Network in Embryonic Stem Cells	0.013803843	0.106414302	GBX2,LHX5,TRIM24,CDX2,HAND1,MEIS1,OTX1,EOMES,STAT3,HOXB1,GSX2,SOX2,ISL1,CDYL,SKIL,GATA4,ZIC3,ZFHX3
RhoA Signaling	0.014125375	0.107398941	MPRIP,SEPT9,MYL2,PIKFYVE,RAPGEF6,ROCK2,PTK2,MYLK,CFL2,PLXNA1,EZR,BAIAP2,CIT,IGF1R,ARHGAP12,PFN2,ARPC1A,ACTG2,MYL10,SEMA3F,ACTR2,NGEF,ARHGEF12,NRP2,CFL1,GNA12,RTKN,ACTB,SEPT7,ARH GAP4,RDX,WASF1,LPAR3,PLD1,ARHGAP5,KTN1,MYL12A,PIP5K1A,RHPN2,RND3,MYL12B,PPP1R12B,CDC42EP4
B Cell Receptor Signaling	0.014454398	0.107894672	RAF1,GAB2,MAP3K11,PIK3R1,PDPK1,KRAS,GSK3A,BCL6,CREB5,PTEN,PAK5,PTPRC,MAP3K10,IKBKG,CAMK2D,MRAS,ETS1,PIK3C2B,MAP3K9,AKT2,CREB3,CREBBP,NFKB2,MALT1,TCF3,ATF2,SYNJ2,PIK3R3,BCL2L1,CAMK2,MAP2K6,RELA,ABL1,MAP3K5,NFKB1,MTOR,NFKBIA,NFAT5,JUN,CARD10,MAP3K7,SOS1,PIK3C2A,FCGR2A,GRB2,MAP3K1,IKBKE,NFAT4C,CALM1 (includes others),MAPK14,FOXO1A,MAP3K12,LYN,NFATC2,MAP3K8,PIK3CB
RAN Signaling	0.014791084	0.108642562	KPNB1,KPNAs1,KPNAs4,KPNAs6,KPNAs2,TNP01,RANGAP1,RANBP2,XPO1
NGF Signaling	0.014791084	0.108642562	RAP1B,RAF1,RELA,MAP3K11,PIK3R1,PDPK1,KRAS,SMPD1,MAP3K5,CREB5,NGF,NFKB1,PRKCZ,ROCK2,MAP3K10,IKBKG,MAP3K7,TRAF4,SOIS1,MRA,SMPD3,PIK3C2B,MAP3K9,AKT2,PIK3C2A,GRB2,MAP3K1,CREB3,CREBBP,PLCG1,IKBKE,NFKB2,ATF2,PIK3R3,RPS6KA6,TRIO,MAP3K8,PIK3CB,RP56KA1
Glioma Signaling	0.015848932	0.113501082	RAF1,PIK3R1,ABL1,CDKN2C,KRAS,RBL1,CCND1,PDGFC,PRKCZ,PTEN,MTOR,CAMK2D,SOS1,MRAS,IGF1R,PRKCE,E2F2,PRKD1,EGFR,PIK3C2B,AKT2,RLB2,PIK3C2A,GRB2,CDK6,PLCG1,MDM2,PDGFB,SIN3A,PRKCG,PIK3R3,CALM1 (includes others),IGF2,PRKCI,PIK3CB,CAMK2G
Neurotrophin/TRK Signaling	0.016595869	0.118850223	MAP2K6,RAF1,BDNF,PIK3R1,PDPK1,KRAS,MAP3K5,CREB5,NGF,JUN,SOS1,MRAS,SORCS1,PIK3C2B,PIK3C2A,SPRY1,GRB2,CREB3,CREBBP,PLCG1,ATF2,PIK3R3,FOS,SPRY2,PIK3CB,RPS6KA1,MAP2K5
Glucocorticoid Receptor Signaling	0.017782794	0.124451461	RAF1,TAF11,JAK1,PRKAB2,PRKAB1,CD3E,SGK1,SMAD3,PIK3R1,KRAS,IL6,KRT32,HSPA5,TGFBR2,HSPA4,IKBKG,HMBG1,MRAS,POLR2H,SERpine1,CDKN1C,IL8,PIK3C2B,STAT5A,SMAD2,AKT2,ME1,CDK7,CREBBP,TBP,STAT3,TAF15,NCOA3,HSPA8,PIK3R3,BCL2L1,DUSP1,TGFb3,HSP90AA1,POLR2I,UBE2I,RELA,PRKCE,NFKB1,NR3C1,SMARCA4,BCL2,GTf2B,HSP90B1,JU,N,NFAT5,NFKBIA,CCL2,HSP90AB1,MAP3K7,ANXA1,SOS1,FOXO3,PRKAA2,CEBPA,TGFb2,NCOR1,STAT5B,STAT1,FKBP5,NOS2,ADR2B,TAF12,PIK3C2A,GRB2,MAP3K1,CHP1,IKBKE,CEBPB,NFAT4C,HSPA2,FOS,TRAF2,SCGB1A1,MAPK14,PRKAG2,NFATC2,PIK3CB,NCOR2,NRIP1,A2M,HLTF
Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis	0.018620871	0.128528666	BMP4,MMP3,AXIN1,PIK3R1,TAB2,CSNK1A1,WNT16,SP7,IL6,TCF7,IKBKG,RUNX2,BIRC3,FZD2,TNFRSF1B,PIK3C2B,AKT2,FZD9,TCF3,GSN,APC,PIK3R3,IL18,BMPR1B,CBL,LEF1,FZD5,SFRP1,MAP2K6,RELA,ADAM17,SFRP2,BMP2,LRP6,BMPR2,IL1F10,MAP3K5,NFKB1,BCL2,NFKBIA,JUN,NFAT5,DKK3,MAP3K7,ITGB1,LRP5,PIK3C2A,ITGA1,WT12,MAP3K12,AKAP1,SMAD6,IKBKE,NFAT4C,ITGA3,BMP5,XIAP,FZD8,CALM1 (includes others),FOS,TRAF2,MAPK14,WNT10A,FOXO1,CSF1,NFATC2,PIK3CB,BMP7,DKK1,BMP6,WNT11,LRP1,TCF7L2,BIRC2
Sertoli Cell-Sertoli Cell Junction Signaling	0.018620871	0.128528666	RAF1,MAP3K11,AXIN1,TGFBR3,MLL74,GSK3A,KRAS,PTEN,OCLN,MAP3K10,CTNNA2,SPTB,MRAS,TUBA1C,MTMR2,ACTG2,JUP,MAP3K9,AKT2,TJP2,TUBA1B,ATF2,CDH1,ZAK,TGFb3,GUCY1A2,ACTN4,SPTAN1,SPTBN1,NOS1,TUBA3E,SYMPK,MAP3K5,BCAR1,JUN,CLDN4,SORBS1,MAP3K7,PPAP2B,PVRL1,NOS2,RAB8B,ITGB1,CLDN10,EPN1,TJP1,ACTB,MAP3K1,ITGA2,ITG A3,EPB41,MAPK14,PRKG1,TUBA1A,CLDN1,PRKAG2,MAP3K8,MAGI2,A2M,CLDN22,CLDN3
Protein Kinase A Signaling	0.019498446	0.131825674	RAF1,SHH,GSK3A,CREB5,PLCH2,GNB1,MYLK,PTPRC,TDP2,CDKN3,MYL1,0,EYA2,PRKD1,PTPRG,PDE2A,PPP1R1B,CREBBP,PTCH1,CREB3,YWHAQ,I,TPR1,NFKB2,TCF3,PTP4A1,CNGA3,ATF2,PDE8A,AKAP13,PTPRH,MYL12A,GNB2,HIST1H1D,CAMK2G,RAF1B,AKAP12,FLNB,HIST1H1C,PDE7A,PDIA3,DUSP6,PPP1R3C,PTPN14,CDC23,AKAP7,GNG7,PRKCF,TIMM50,DUSP5,HAT,PTPRJ,PRKCE,CNGB3,GNB1L,MTMR3,PTPRK,PLCG1,PRKCG,CALM1 (includes others),GNAI3,PPP1R14D,CDC14B,SNF,EYA1,CDC27,TCF7L2,AKAP1,MYL2,SMAD3,GNB2L1,TCF7,PTEN,TGFBR2,PTK2,YWHAQ,ROCK2,PLCD3,TH,CAMK2D,PLCE1,PDE7B,RYR3,HIST1H1B,ADCY9,ITPR2,PDE10A,PTPDC1,MYL12B,DUSP1,TGFb3,PTPRs,LEF1,RELA,H3F3A/H3F3B,ANAPC1/ANAPC1 P1,PDE4A,NFKB1,NFAT5,GNG11,NFKBIA,GLI3,DUSP10,PTPN1,TGFb2,VA SP,PXN,ATF1,MAP3K1,CHP1,GNA11,AKAP6,PYGB,NFAT4C,PDE4D,GNG5, GNA12,PRKCI,PRKAG2,NFATC2,PTPDC2,PDE5A
FLT3 Signaling in Hematopoietic Progenitor Cells	0.020417379	0.134276496	GAB2,RAF1,PIK3R1,PDPK1,KRAS,CREB5,MTOR,SOS1,MRAS,STAT1,STAT5B,PIK3C2B,STAT5A,AKT2,PIK3C2A,GRB2,CREBBP,CREB3,STAT3,ATF2,S TAT4,PIK3R3,RPS6KA6,CBL,MAPK14,PIK3C2B,RPS6KA4,RPS6KA1
Induction of Apoptosis by HIV1	0.020417379	0.134276496	RELA,SLC25A13,CYCS,IKBKE,NFKB2,MAP3K5,NFKB1,DDFA,BAK1,XIAP,BCL2,FADD,BCL2L1,TRAF2,IKBKG,NFKBIA,BBC3,BID,SLC25A10,CASP8,BIR C3,FASLG,TNFRSF1B,BIRC2
Cell Cycle: G1/S Checkpoint Regulation	0.020417379	0.134276496	HDAC9,CCNE2,RBL2,HDAC4,HDAC8,HDAC2,SMAD3,HDAC1,ABL1,CDK6,M DM2,RBL1,CCND1,SKP1/SKP1P2,SIN3A,HDAC5,MYC,CCNE1,MAX,TGFb3, TGFb2,BTRC,ATR,E2F2
CREB Signaling in Neurons	0.022387211	0.144543977	RAF1,GRIN2A,GRM3,PIK3R1,GNB2L1,KRAS,CREB5,PLCH2,GRIA4,GNB1,PLCD3,PLCE1,CAMK2D,GNAT1,MRAS,PLR2H,PRKD1,GRIK1,ADCY9,PIK3C2B,AKT2,ITPR2,CREB3,CREBBP,TBP,ITPR1,ATF2,PIK3R3,GNAO1,GNB2, RPS6KA1,PLR2I,GNAL,CAMK2G,PDIA3,PRKCF,GNG7,GTf2B,GNG11,GRI D1,SOS1,PRKCE,GRIK2,GNB1L,GRIN2B,PIK3C2A,GRB2,GNA12,GNB1,PL CG1,GNG5,PRKCG,GNA12,CALM1 (includes others),GNAI3,PRKCI,GRIK4,PRKAG2,PIK3CB
Role of JAK family kinases in IL-6-type Cytokine Signaling	0.023988329	0.151356125	IL6ST,SOCS1,SOCS3,STAT5A,JAK1,MAPK14,IL6R,OSMR,STAT3,IL6,STAT1,STAT5B
VDR/RXR Activation	0.024547089	0.151705037	SERPINB1,CYP24A1,CCNC,HES1,PRKCF,GTf2B,GADD45A,SP1,RUNX2,CEBPA,CSNK2A1,TGFb2,PRKCE,NCOR1,SEMA3B,IGFBP1,PRKD1,W1,LRP5,PPARD,ME1,CEBPB,NCOA3,PRKCG,PRKCI,FOXO1,COL13A1,IGFBP3,N COR2,HSD17B2
Regulation of IL-2 Expression in Activated and Anergic T Lymphocytes	0.024547089	0.151705037	RELA,RAF1,CD3E,SMAD3,KRAS,NFKB1,TGFb2,CD28,IKBKG,NFAT5,JUN,NFKBIA,SOS1,TGFb2,MRAS,SMAD2,GRB2,CHP1,MAP3K1,TOB1,PLCG1,IKBKE,NFKB2,MALT1,NFATC4,FOS,CALM1 (includes others),GNAI3,PRKCI,GRIK4,PRKAG2,PIK3CB

			others),BCL10,TGFB3,NFATC2
BMP signaling pathway	0.025118864	0.153461698	REL1,RAF1,BMP4,BMP2,BMPR2,KRAS,HOXA9,NFKB1,NOG,JUN,RUNX2,MAP3K7,SOS1,MRAS,FST,GRB2,CREBBP,SMAD6,SMAD7,NFKB2,BMP5,XIA
G Beta Gamma Signaling	0.027542287	0.169044093	PI,ATF2,BMPR1B,MAPK14,PRKAG2,BMP7,BMP6 RAF1,GNB2L1,PDPK1,KRAS,GNG7,PRKCZ,GNB1,GNG11,GNAT1,SOS1,CAV1,MRAS,PRKCE,CAV2,GNB1L,PRKD1,EGFR,AKT2,GRB2,GNA12,GNA11,P,LCG1,KCNJ3,GNG5,PRKCG,GNA12,GNA13,PRKCI,ARHGEF6,GNAO1,GNB2,PRKAG2,GNAL
TR/RXR Activation	0.028183829	0.170215851	NXPH2,PIK3R1,HIF1A,DIO2,NRGN,SLC16A3,MTOR,ADRB1,SCARB1,FASN,NCOR1,TBL1XR1,PIK3C2B,AKT2,UCP2,PIK3C2A,GP52,SLC2A1,MED1,MDM2,THRA,PFKP,THRSP,NCOA3,PIK3R3,COL6A3,SREBF1,ENO1,SREBF2,PIK3CB,NCOR2,THRB
Oncostatin M Signaling	0.028840315	0.171001532	IL6ST,MT2A,STAT5A,RAF1,EPAS1,JAK1,MMP3,GRB2,KRAS,STAT3,SOS1,MRAS,OSMR,STAT5B,STAT1 MAP2K6,RAF1,KRAS,IL1F10,BCAR1,RHOH,PRKCZ,ROCK2,PTK2,JUN,RHOB,RHOT1,SOS1,RHOU,MRAS,SST,PRKCE,RHOF,PRKD1,EGFR,PXN,MEF2BNB-
Cholecystokinin/Gastrin-mediated Signaling	0.030199517	0.17538805	MEF2B,GRB2,ITPR2,GNA12,MEF2A,ITPR1,PRKCG,ATF2,FOS,IL18,MAPK14,PRKCI,RND3,MEF2C,MAP2K5,FNBP1 SHH,BMP4,GLI2,AXIN1,BMP2,WNT16,TCF7,HKR1,GLI3,FZD2,GLIS1,WNT2B,PTCH1,FZD9,TCF3,BMP5,APC,FZD8,GLIS2,WNT10A,LEF1,FZD5,BMP7,D,VL2,BMP6,TCF7L2,WNT11
Basal Cell Carcinoma Signaling	0.030199517	0.17538805	RAF1,RELA,F2RL2,MYL2,PIK3R1,KRAS,MAP3K5,NFKB1,CDH11,PTK2,ROCK2,IKBKG,CDH7,NFKBIA,JUN,F2RL1,CDH3,MRAS,MYL10,PIK3C2B,PXN,AKT2,PIK3C2A,MEF2BNB- MEF2B,GNA12,MAP3K1,CDH6,MEF2A,CDH18,IKBKE,NFKB2,LPAR3,PIK3R3,CDH1,MYL12A,CDH2,CDH9,CDH12,MYL12B,CDH8,PIK3CB,MEF2C
Gα12/13 Signaling	0.030902954	0.17538805	CDK7,WEE1,YWHAZ,MDM2,RPRM,SKP1/SKP1P2,CDK1,PRKCE,CHEK1,YWHAQ,MDM4,GADD45A,CKS1B,TOP2A,BTRC,RPS6KA1,SNF1,ATR AHCYL1,SUV39H2,MGMT,PRMT5,FTSJ1,MAT2B,MAT2A,AHCY
Cell Cycle: G2/M DNA Damage Checkpoint Regulation	0.030902954	0.17538805	IL6ST,PIK3C2B,RAF1,JAK1,PIK3C2A,GRB2,PIK3R1,CNTFR,KRAS,STAT3,LI FR,PIK3R3,MTOR,RPS6KA6,SOS1,MRAS,PIK3CB,RPS6KA4,RPS6KA1,STA T1
Methionine Degradation I (to Homocysteine)	0.031622777	0.17538805	ITGB1,PAK4,ARHGEF12,PAK2,CFL1,DPYSL3,DPYSL4,RHOH,ROCK2,PTK2, MET,SEMA3A,CFL2,RND3,RHOB,RHOT1,PLXNA1,RHOU,RHOF,FNBP1,NR P1
CNTF Signaling	0.031622777	0.17538805	RAF1,EIF2B4,PIK3R1,EIF1,KRAS,HIF1A,PDGFC,ELAVL1,BCL2,ARNT,VEGFA,PTK2,ROCK2,EIF1AX,FOXO3,SOS1,MRAS,VCL,ACTG2,PIK3C2B,PXN,AKT2,PIK3C2A,GRB2,ACTB,VEGFC,PLCG1,PIK3R3,BCL2L1,FOXO1,PIK3CB,A CTN4,SNF
Semaphorin Signaling in Neurons	0.031622777	0.17538805	RAF1,F2RL2,JAK1,PDIA3,PIK3R1,PDPK1,KRAS,PLCH2,PRKCZ,YWHAQ,PLCD3,MTOR,PLCE1,F2RL1,SOS1,PPM1L,MRAS,PRKCE,PPP2R2K,PRKD1,EGFR,PIK3C2B,AKT2,PIK3C2A,GRB2,GNA11,YWHAZ,PLCG1,PLD1,PRKCG,GNA2,PIK3R3,GNA13,PRKCI,IRS1,PPP2R2B,LYN,PIK3CB,PPP2R5E,SNF,AGTR1
p70S6K Signaling	0.035481339	0.192309173	RAF1,GAB2,RAPGEF1,JAK1,PIK3R1,KRAS,PRKCZ,JUN,SOS1,MRAS,PRKE,STAT1,STAT5B,PRKD1,PIK3C2B,STAT5A,AKT2,PIK3C2A,GRB2,CHP1,STAT3,PRKCG,PIK3R3,FOS,PRKCI,FOXO1,PIK3CB
IL-3 Signaling	0.036307805	0.195433946	RAP1B,RAPGEF1,MYL2,TUBA3E,TGFBP3,BMPR2,MLLT4,KRAS,MYH11,CLIP1,TCF7,PTEN,TGFBR2,CTNNA2,WSNL,SORBS1,HGF,BAIAP2,TGFBR2,MRA P,SVRL1,ARPC1A,TUBA1C,VCL,JUP,ACTG2,ACVR1C,EGFR,ACTR2,EPN1,DLL1,AKT2,LMO7,ACTB,WASF1,TCF3,TUBA1B,APC,ACVR1B,MET,CDH2,C DH1,TUBA1A,MYH3,MYH9,LEF1,ACTN4,MAGI2,TCF7L2,CTNND1
Epithelial Adherens Junction Signaling	0.037153523	0.195433946	PIK3R1,KRAS,ITGB8,NGF,PDGFC,PRKCZ,ARF6,HGF,MRAS,PRKCE,ITGB4,ITGB5,PRKD1,ITGB1,PIK3C2B,PIK3C2A,PLCG1,PDGFB,PRKCG,MET,PIK3R3,PRKCI,CSF1,PIK3CB,ACTN4,ITGB6
Macropinocytosis Signaling	0.037153523	0.195884467	RELA,IKBKE,IL6,CEBPB,NFKB2,NFKB1,FOS,IKBKG,TRAF3IP2,NFKB1A,JUN,MAPK14,CCL2,MAP3K7
IL-17A Signaling in Fibroblasts	0.03801894	0.195884467	RAF1,CSNK1G1,CD3E,PIK3R1,GNB2L1,CSNK1A1,GSK3A,KRAS,GNB1,CD28,IKBKG,GNAT1,MRAS,XP01,PIK3C2B,AKT2,ITPR2,CSNK1D,ITPR1,NFKB2,ATF2,PIK3R3,GNAO1,GNB2,RCAN3,GNAL,RELA,NFKB1,GNG7,NFKBIA,JUN,NFAT5,GNG11,SOS1,GNB1L,PIK3C2A,MEF2BNB- MEF2B,GRB2,FCGR2A,GNA12,CSNK1G3,CHP1,GNA11,MEF2A,PLCG1,IKBKE,NFAT4,CNG5,GNA12,FOS,CALM1 (includes others),GNA13,LYN,NFATC2,MEF2C,PIK3CB,GATA4
Role of NFAT in Regulation of the Immune Response	0.03801894	0.195884467	PIK3C2B,RAF1,AKT2,JAK1,PIK3C2A,ITPR2,GRB2,PIK3R1,MAP3K1,PLCG1,I TPR1,STAT3,PIK3R3,FOS,MTOR,JUN,MAPK14,SOS1,CSNK2A1,PIK3CB,STAT1,EGFR
EGF Signaling	0.038904514	0.198609492	RAF1,MYL2,PIK3R1,GNB2L1,KRAS,ROCK2,PTK2,GNB1,RHOH,GNAT1,MRA S,MYL10,PRKD1,ADCY9,PIK3C2B,AKT2,ITPR2,ITPR1,PIK3R3,MYL12A,RND3,MYL12B,GNAO1,GNB2,ELMO1,FNBP1,GNAL,BCAR1,RHOH,PRKCZ,GNG7,JUN,GNG11,RHOT1,RHOH,PRKCZ,GNB1L,RHOH,PXN,PAK4,PAK2,PIK3C 2A GNA12,GNA11,GNG5,PRKCG,GNA12,FOS,GNA13,PRKCI,LYN,PIK3CB
CXCR4 Signaling	0.038904514	0.198609492	RAF1,MPIP1,MYL2,CD3E,GNB2L1,KRAS,CREB5,GNB1,PLCE1,RHOB,MRA S,MYL10,PRKD1,ADCY9,HDAC4,HDAC8,ITPR2,CREBBP,NF KB2,ITPR1,PLD1,ATF2,HDAC5,PLA2G6,MYL12A,RND3,MYL12B,ARHGEF16,ARHGEF6,GNB2,PPP1R12B,ARHGEF9,FNBP1,RAP1B,RELA,NAPEPLD,NF KB1,RHOH,PRKCZ,GNG7,TGM2,GNG11,NFAT5,AHNK,ARHGEF1,CDH1,HDAC9,ARHGEF12,ME F2BNB- MEF2B,FCGR2A,GRB2,ITGA2,HDAC1,CHP1,MEF2A,PLCG1,NFAT4,ITGA3 ,GNG5,PRKCG,PLA2G4A,CALM1 (includes others),PRKCI,LYN,NFATC2,MEF2C
Phospholipase C Signaling	0.040738028	0.206062991	MAP2K6,RELA,TAB2,GNB2L1,NFKB1,GNG7,IRAK1,GNB1,IKBKG,GNG11,JU N,NFKBIA,GNAT1,MAP3K7,MRAS,GNB1L,ADCY9,GNA12,MAP3K1,GNA11,IK BKE,NFKB2,GNG5,GNA12,FOS,MAPK14,GNAO1,GNB2,PRKAG2,IRA K4,GNAL,IRAK2
IL-1 Signaling	0.044668359	0.222330989	CTGF,PIK3R1,CXCL1,KRAS,PTEN,VEGFA,MTOR,ARRB1,CFL2,F2RL1,ITGA V,MRAS,STAT5B,ITGB5,EGFR,ITGB1,STAT5A,PIK3C2B,IL8,AKT2,PIK3C2A, CFL1,GNA12,ITGA6,VEGFC,ITGA3,F3,PIK3R3,BCL2L1,RPS6KA6,MAP K14,CNG5,LYN,RPS6KA4,PIK3CB,RPS6KA1,CYR61
Role of Tissue Factor in Cancer	0.045708819	0.223357222	

Lymphotxin β Receptor Signaling	0.047863009	0.234422882	RELA,PIK3C2B,TRAF3,AKT2,PIK3C2A,CYCS,PIK3R1,CREBBP,CXCL1,PDPK1,IKBKE,NFKB2,NFKB1,PIK3R3,BCL2L1,IKBKG,TRAF2,NFKBIA,TRAF4,PIK3CB,BIRC2
Ephrin A Signaling	0.048977882	0.234422882	EPHA7,PIK3C2B,NGEF,PIK3C2A,CFL1,PIK3R1,EFNA3,BCAR1,EFNA4,EFNA1,PIK3R3,ROCK2,PTK2,EPHA6,CFL2,EFNA5,EPHA5,PIK3CB,EPHA2
Docosahexaenoic Acid (DHA) Signaling	0.048977882	0.234422882	PIK3C2B,AKT2,PIK3C2A,CYCS,PIK3R1,SERPINF1,PDPK1,GSK3A,PNPLA2,APP,BCL2,PIK3R3,BCL2L1,FOXO1,BID,PIK3CB
Ceramide Signaling	0.048977882	0.234422882	RAF1,RELA,PIK3R1,SMPD1,KRAS,NFKB1,PRKCZ,KSR1,BCL2,JUN,PPM1L,MRAS,PPP2R2C,SMPD3,NSMAF,TNFRSF11B,PIK3C2B,AKT2,PIK3C2A,CYCS,MAP3K1,NFKB2,PIK3R3,FOS,PPP2R2B,S1PR1,PIK3CB,PPP2R5E,ENPP7

Supplementary Table 10: All HEK293 TCF7L2 Ingenuity Conical pathways with at least nominal $P < 0.05$

Canonical Pathways	P-value	B-H Multipule testing correction p-value	Molecules
Wnt/ β -catenin Signaling	1.8197E-10	9.33254E-08	CDKN2A,TGFBR3,CSNK1A1,WNT16,TLE1,BCL9,SOX13,CCND1,TCF7,MYC,TGFB R2,SOX2,RARA,CSNK2A1,DKK2,SOX4,AKT2,AXIN2,GJA1,TCF3,CDH2,CDH12,CD H5,TGFB3,TLE3,FZD3,SOX8,LEF1,FZD10,TCF4,SFRP2,SOX1,FZD1,KREMEN1,EP 300,SOX17,SOX9,NLK,JUN,MAP3K7,SOX3,RARB,SOX14,PPP2R5C,SOX18,CTNN B1,ACVR1C,SOX5,PPARD,CSNK1G3,WNT2B,PPP2R5A,FZD8,WNT8A,FZD4,WNT 10A,SOX6,TLE4,NR5A2,BTRC,DKK1,PPP2R5E,PPP2R1B,ACVR2A,WNT11,TCF7L 2,FZD7,WNT5A
Factors Promoting Cardiogenesis in Vertebrates	6.91831E-07	0.000177828	FZD10,TCF4,BMP4,TGFB3,BMP2,FZD1,NOC,TCF7,TGFB2,MAP3K7,PRKCE,CT NN1,ACVR1C,PRKD1,PRKCA,TBX5,PRKCQ,TCF3,BMP5,ATF2,FZD8,CCNE1,BM PR1B,MAPK14,FZD4,FZD3,TGFB3,MEF2C,LEF1,BMP7,PRKCH,DKK1,BMP6,WNT1 1,ACVR2A,TCF2,FZD7
Human Embryonic Stem Cell Pluripotency	2.75423E-06	0.000467735	BMP4,PIK3R1,SMAD3,WNT16,TCF7,SOX2,TGFB2,PIK3C2B,AKT2,FGFR2,TCF3,I NHBA,BMPR1B,TGFB3,FZD3,LEF1,FZD10,TCF4,KLK3,FGF2,BDNF,BMP2,FZD1,N GF,PDGFC,NOG,PIK3C3,CTNNB1,PIK3C2A,WNT2B,SMAD7,PIK3C2G,SMAD6,BM P5,FZD8,WNT8A,FZD4,FOXO1,WNT10A,NTRK3,S1PR1,PIK3C2B,BMP7,WNT 11,TCF7L2,FZD7,WNT5A,SALL4
Axonal Guidance Signaling	7.4131E-06	0.000954993	SLT3,SHH,GLI2,BMP4,PIK3R1,NTN1,GNB1,EPHB1,BAIAP2,PLCB1,SRGAP2,PLCL 1,PRKD1,GNG12,ITGA4,PIK3C2B,AKT2,PRKCQ,KALRN,SEMA5A,PTCH1,SRGAP3 ,ADAMTS6,RTN4,EPHA2,NRP1,RAP1B,FYN,BDNF,SEMA6A,EPHA4,PLXNA2,FZD1 ,ABLM1,EIF4E,GNG7,EFNB2,ACTR3,PLXNA1,PIK3C3,EFNA5,DCC,PRKCE,PSMD14,ROBO2,PPP3CA,UNC5C,GLIS1,ITGB1,NRP2,GRB2,PIK3C2G,EPHA3,SLI T2,EFNA1,PLCZ1,SEMA3A,NTRK3,EPHA5,BMP7,SEMA3C,BMP6,FZD7,UNC5B,G NB2L1,CXCL12,WNT16,PTK2,PLCE1,SEMA3D,SUFU,ADAM28,PROK1,PPP3R1,A DAMTS5,EPHA7,ADAMTS1,VEGFC,ADAMTS9,ADAM12,PTPN11,SEMA6D,FZD3,P RKCH,ERAP2,FZD10,ADAMTS7,BMP2,NGF,PDGFC,ROBO1,WASL,EPHA8,GLI3,S EMA3B,PRKCA,SEMA3E,ARHGEF12,PLXNC1,PIK3C2A,C9orf3,WNT2B,GNAI1,EF NA3,BMP5,PLXND1,EFNA4,ROCK1,FZD8,WNT8A,PLCB4,FZD4,WNT10A,NFATC2 ,PIK3C2B,WNT11,PRKAR1A,WNT5A
Basal Cell Carcinoma Signaling	1.99526E-05	0.002041738	FZD10,SHH,TCF4,GLI2,BMP4,BMP2,WNT16,FZD1,TCF7,GLI3,SUFU,CTNNB1,GLI S1,WNT2B,PTCH1,TCF3,BMP5,FZD8,WNT8A,FZD4,WNT10A,FZD3,LEF1,BMP7,B MP6,WNT11,TCF7L2,FZD7,WNT5A
FGF Signaling	9.54993E-05	0.007762471	MAP2K6,FGF2,PIK3R1,FGF8,MAP3K5,CREB5,FGF13,EP300,FGF18,PIK3C3,HGF ,FGF12,FRS2,PRKCA,FGF19,FGF16,PIK3C2B,AKT2,PIK3C2A,GRB2,FGF9,MAP3K1 ,PIK3C2G,FGFR2,ITPR1,FGF1,ATF2,MET,MAPK14,PTPN11,PIK3C2B,RP56KA5
Ephrin A Signaling	0.000107152	0.007762471	EPHA7,FYN,PIK3C2B,PIK3C2A,PIK3R1,EFNA3,PIK3C2G,EPHA4,EPHA3,EFNA4,E FNA1,ROCK1,PTK2,EPHA8,PTPN11,PIK3C3,VAV3,EFNA5,EPHA5,PIK3C2B,EPHA2
Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis	0.00020893	0.013182567	BMP4,PIK3R1,TAB2,CSNK1A1,WNT16,SP7,IL6,TCF7,IKBBK,RUNX2,PPP3R1,DKK 2,TRAF5,ADAMTS5,PIK3C2B,AKT2,TCF3,IL7,BMPR1B,FZD3,LEF1,MAP2K6,FZD10 ,TCF4,SFRP2,BMP2,FZD1,MAP3K5,NFKB1,JUN,MAP3K7,PIK3C3,CTNNB1,PPP3C A,ITGB1,CTSK,PIK3C2A,WNT2B,DLX5,SMAD6,PIK3C2G,IKBKE,TNFRSF11A,BMP 5,XIAP,IL17A,FOS,FZD8,WNT8A,MAPK14,FZD4,WNT10A,FOXO1,CSF1,NFATC2,IL 1B,BMP2,PIK3CB,DKK1,BMP6,WNT11,TCF7L2,WNT5A,FZD7
Protein Kinase A Signaling	0.000331131	0.016982437	SHH,CREB5,NTN1,GNB1,PTPRC,PLCB1,CDKN3,PLCL1,EYA2,PRKD1,GNG12,PTP RG,PRKCQ,PTCH1,ITPR1,TCF3,PTP4A1,CNGA3,ATF2,PDE8A,AKAP13,PTPRB,C REM,EYA3,DUSP4,PTPRA,AKAP12,RAP1B,FLNB,TCF4,PTPN13,DUSP6,PTPN14 ,CDC23,GNG7,EP300,DUSP5,HHAT,DCC,CNGB3,CTNNB1,PPP3CA,MTMR 3,AKAP5,PTPRK,PLCZ1,ADD3,CDC14B,EYA1,PTPRT,TCF7L2,PDE3A,SMAD3,GN B2L1,TCF7,PTEN,PTK2,YWHAQ,TGFB2,PLCE1,CAMK2D,ADCY5,PPP3R1,PDE1 1A,PPP1R14C,PTPRD,YWHAE,ITPR2,PTPDE10A,PTPDE4B,EPM2A,PTPN11,TGFB3,PP P1R12A,PRKCH,LEF1,PDE4A,NFKB1,PHKA2,GLI3,DUSP10,PTPN1,PRKCA,RYR2 ,MAP3K1,GNAA1,PYGB,AKAP6,PDE4D,ROCK1,AKAP2/PALM2-A,AKAP2,PLC4,BMP2,PTPNU,NFATC2,AKAP1,AKAP9,PRKAR1A
Mouse Embryonic Stem Cell Pluripotency	0.000338844	0.016982437	IL6ST,FZD10,TCF4,ID2,BMP4,LIF,T,PIK3R1,FZD1,TCF7,SOX2,MYC,ID1,MAP3K7,P IK3C3,CTNNB1,PIK3C2B,AKT2,PIK3C2A,GRB2,PIK3C2G,TCF3,XIAP,FZD8,MAPK1 4,FZD4,PTPN11,FZD3,PIK3C2B,LEF1,TCF7L2,D4,FZD7
Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	0.000371535	0.016982437	TRAF3,PIK3R1,CSNK1A1,CXL12,WNT16,IL6,CREB5,CCND1,TCF7,MYC,IKBKB,T RAF3IP2,PLCE1,CAMK2D,PROK1,PPP8R1,TRAF4,PLCB1,DKK2,TRAF5,PLCL1,PR KD1,PIK3C2B,AKT2,PRKCQ,IL6R,VEGFC,TCF3,IL7,ATF2,FZD3,PRKCH,LEF1,IL6S T,MAP2K6,FZD10,TCF4,SFRP2,Fn1,FGF2,FZD2,NFKB1,PDGFC,EP300,ROR2,NLK ,JUN,MAP3K7,PIK3C3,CEBPA,PRKCE,NOS2,CTNNB1,PPP3CA,PRKCA,PIK3C2A ,WNT2B,DAAM1,PIK3C2G,IKBKE,IL17A,PLCZ1,ROCK1,FZD8,FOS,PLCB4,WNT8A ,MAPK14,FZD4,WNT10A,TLR5,CSF1,NFATC2,IL1B,PIK3CB,DKK1,WNT11,TCF7L2 ,FZD7,WNT5A
Role of NFAT in Cardiac Hypertrophy	0.000457088	0.016982437	LIF,CAMK1D,PIK3R1,GNB1,CSNK1A1,HAND1,IL6,CABIN1,TGFB2,GNB1,PLCE 1,CAMK2D,ADCY5,PPP3R1,PLCB1,PLCL1,PRKD1,GNG12,PIK3C2B,AKT2,HDAC4 ,PRKCQ,HDAC2,HDAC8,ITPR2,ITPR1,TCF4,PRKCH,SLC8A1,MAP2K6,IL6ST,GN G7,EP300,MAP3K7,PIK3C3,IGF1R,CAMK1G,PRKCE,PPP3CA,PRKCA,AKAP5,PIK3 C2A,GRB2,MAP3K1,GNAA1,PIK3C2G,PLCZ1,PLCB4,MAPK14,MEF2C,PIK3CB,RCA N2,PRKAR1A
p53 Signaling	0.000501187	0.016982437	CDKN2A,JMY,GADD45G,PIK3R1,CCND1,EP300,PTEN,JUN,GADD45A,BBC3,PIK3 C3,CCNK,ADCK3,CTNNB1,W71,PIK3C2B,PMAIP1,AKT2,TP63,PIK3C2A,MED1,PIK 3C2G,PERP,RPRM,TP53BP2,KAT2B,MAPK14,CCND2,SNAI2,PIK3CB,ATR,DRAM1
VDR/RXR Activation	0.000501187	0.016982437	SERPINB1,CYP24A1,HE51,EP300,GADD45A,RUNX2,CEBPA,CSNK2A1,PRKCE,S EMA3B,CALB1,PRKD1,PRKCA,W71,PRKCH,MED1,PPARD,IGFBP5,KLF4,SULT2A 1,COL13A1,FOXO1,NCOA1,IGFBP3,PRKCH,NCOR2,RXRA,S100G
Xenobiotic Metabolism Signaling	0.000524807	0.016982437	LIPC,CAMK1D,PIK3R1,MAF,IL6,CHST15,ARNT,MOAB,CAMK2D,CHST11,HS3ST1 ,AHR,PRKD1,PIK3C2B,PRKCQ,HDAC4,MED1,ALDH8A1,GRIP1,NDST4,SULT2A1,H S3ST3B1,ALDH1A2,NCOA1,HSP90AA1,PRKCH,RXRA,HS3ST5,MAP2K5,MAP2K6 ,CHST7,NCOQ2,HS2ST1,ALDH1A1,MAP3K5,FM05,NFKB1,EP300,CUL3,MAP3K7,PIK 3C3,CAMK1G,HS6ST2,PRKCE,FM01,PPP2R5C,NOS2,NFE2L2,CITED2,PRKCA,G STA3,PIK3C2A,MGMT,GSTA4,MAP3K1,PIK3C2G,CHST12,CYP1B1,PPP2R5A,ESD

Molecular Mechanisms of Cancer	0.000562341	0.016982437	,SULT2B1,MAPK14,MGST2,HS3ST2,IL1B,PIK3CB,MAP3K8,NCOR2,PPP2R5E,PPP2R1B,DNAJC7,MAOA,PPARGC1A
Glioblastoma Multiforme Signaling	0.000588844	0.016982437	CDKN2A,RAPGEF1,SHH,BMP4,SMAD3,DIRAS3,PIK3R1,TAB2,CCND1,MYC,TGFB2,PTK2,E2F6,CTNNNA2,CAMK2D,RHOB,SUFU,ADCY5,PLCB1,PRKD1,PIK3C2B,AKT2,PRKCQ,PTCH1,CDK6,TCF3,RALBP1,RASGRF2,BMPR1B,CCND3,CCND2,PTPN11,ARHGEF16,IRS1,TGFB3,FZD3,PRKCH,LEF1,MAP2K6,RAP1B,FYN,FZD10,TCF4,BMP2,PSEN2,MAP3K5,FZD1,E2F3,NFKB1,CDKN2B,EP300,JUN,HHAT,NLK,B,BC3,MAP3K7,PIK3C3,RHOU,PRKCE,BID,CASP8,CTNNB1,PRKCA,PMAP1,ARHGEF12,PIK3C2A,GRB2,GNAI1,SMAD7,PIK3C2G,SMAD6,BMP5,XIAP,FZD8,FOS,PLC4,CCNE1,MAPK14,FZD4,FOXO1,RPB1,PIK3CB,BMP7,BMP6,ATR,BCL2L11,PRKA1,PISEN1,FZD7,WNT5A
Aryl Hydrocarbon Receptor Signaling	0.000588844	0.016982437	CDKN2A,HSPB3,NFX1,NQO2,ALDH1L1,IL6,NFKB1,CCND1,SMARCA4,EP300,ARN,T,MYC,NR2F1,TGM2,JUN,RARA,RARB,NFE2L2,AHR,GSTA3,MED1,GSTA4,CDK6,ALDH8A1,CYP1B1,FOS,CCNE1,CCND2,CCND3,MGST2,NFIA,ALDH1A2,TGFB3,H,SP90AA1,IL1B,NFIB,DHFR,NCOR2,DCT,RXRA,ATR,ESR1
Transcriptional Regulatory Network in Embryonic Stem Cells	0.000724436	0.019498446	GBX2,LHX5,CDX2,HAND1,MEIS1,OTX1,EOMES,HOXB1,FOXC1,SOX2,ISL1,KAT6A,CDYL,PAX6,GATA6,SIX3,ZFHX3
Neuropathic Pain Signaling In Dorsal Horn Neurons	0.000776247	0.019952623	CAMK1D,GRM3,BDNF,PIK3R1,GRIA1,GRIA4,TACR1,PLCE1,CAMK2D,GPR37,PIK3C3,CAMK1G,PLCB1,PRKCE,PLC1L1,PRKD1,PRKCA,GRIN2B,PIK3C2B,PRKCQ,PIK3C2A,GRM8,ITPR2,PIK3C2G,ITPR1,GRIN3A,PLCZ1,FOS,PLCB4,PIK3CB,PRKCH,PRKAR1A,GRIA3
Heparan Sulfate Biosynthesis	0.000977237	0.023988329	CHST7,XYLT1,HS2ST1,EXT1,CHST12,GLCE,NDST4,CHST15,SULT2A1,SULT2B1,HS3ST3B1,EXT2,HS3ST2,CHST11,B3GAT1,HS6ST2,EXTL3,HS3ST1,EXTL2,B3GA2T2,HS3ST5
Role of Oct4 in Mammalian Embryonic Stem Cell Pluripotency	0.001202264	0.027542287	NR6A1,FOXA1,FAM208A,BMI1,PHC1,CDX2,NR2F2,SH3GLB1,HOXB1,PARP1,SOX2,NR2F1,FOXA2,RARA,JARID2,NR5A2,NR5A1,SALL4
Neurotrophin/TRK Signaling	0.00128825	0.028183829	MAP2K6,PIK3C2B,PIK3C2A,KLK3,BDNF,GRB2,SPRY1,PIK3R1,PIK3C2G,MAP3K5,CREB5,NGF,EP300,ATF2,FOS,JUN,PTPN11,NTRK3,PIK3C3,SPRY2,SORCS1,PIK3CB,FRS2,MAP2K5
Small Cell Lung Cancer Signaling	0.001348963	0.028840315	NOS1,PIK3C2B,AKT2,TRAF3,PIK3C2A,PIK3R1,PIK3C2G,CDK6,IKBKE,NFKB1,CDKN2B,CCND1,PTEN,PTK2,MYC,IKBKB,CCNE1,PIK3C3,RARB,TRAFA4,CKS1B,BID,PIK3C8,TRAF5,RXA
Role of NANOG in Mammalian Embryonic Stem Cell Pluripotency	0.002344229	0.047863009	IL6ST,FZD10,BMP4,LIF,T,PIK3R1,BMP2,WNT16,FZD1,SOX2,PIK3C3,GATA6,CTNNB1,PIK3C2B,AKT2,PIK3C2A,GRB2,WNT2B,CDX2,PIK3C2G,BMP5,FZD8,WNT8A,B,MPR1B,FZD4,WNT10A,FZD3,PIK3CB,BMP7,BMP6,WNT11,SALL4,FZD7,WNT5A
Heparan Sulfate Biosynthesis (Late Stages)	0.002818383	0.054954087	CHST7,HS2ST1,EXT1,CHST12,GLCE,NDST4,CHST15,SULT2A1,SULT2B1,HS3ST3B1,EXT2,HS3ST2,CHST11,HS6ST2,EXTL3,HS3ST1,EXTL2,HS3ST5
Ovarian Cancer Signaling	0.003019952	0.057543994	CDKN2A,FZD10,TCF4,PIK3R1,LHCGR,WNT16,FZD1,CCND1,PDGFC,TCF7,PTEN,ARRB1,EDN1,PROK1,PIK3C3,CTNNB1,PIK3C2B,GRB2,AKT2,PIK3C2A,FGF9,WNT2B,PIK3C2G,VEGFC,TCF3,FZD8,WNT8A,FZD4,WNT10A,FZD3,MSH6,EDNRA,LEF1,PIK3CB,WNT11,TCF7L2,PRKAR1A,FZD7,WNT5A
HGF Signaling	0.003388442	0.0616595	RAP1B,CDKN2A,RAPGEF1,PIK3R1,ETS2,MAP3K5,IL6,CCND1,PTK2,JUN,MAP3K7,PIK3C3,HGF,PRKCE,PRKD1,PRKCA,ETS1,PIK3C2B,AKT2,PRKCQ,PIK3C2A,GRB2,MAP3K1,PIK3C2G,ATF2,MET,FOS,PTPN11,MAP3K8,PIK3CB,PRKCH
Prolactin Signaling	0.004677351	0.081283052	PIK3C2B,FYN,PRKCQ,PIK3C2A,GRB2,PRK1,PIK3R1,SOCS2,PIK3C2G,NR3C1,TCF7,EP300,MYC,FOS,JUN,PTPN11,PIK3C3,IRS1,PRKCE,PIK3CB,NNI,PRKCH,PRKD1,PRKCA
ILK Signaling	0.004786301	0.081283052	MAP2K6,FLNB,FN1,BMP2,DIRAS3,PIK3R1,MYH11,NFKB1,CREB5,PDGFC,CCND1,EP300,PTEN,PTK2,MYC,JUN,RHOB,PROK1,PPAP2B,PIK3C3,RHOU,PPP2R5C,IRS2,CTNNB1,NOS2,DSP,ITGB1,PIK3C2B,PARVA,AKT2,PIK3C2A,TMSB10/TMSB4X,FERMT2,PIK3C2G,VIM,VEGFC,PPR2R5A,ATF2,FOS,LIMS1,IRS1,SNAI2,SH2B2,M,YH3,PPBP1R12A,PPS6K5A,PIK3CB,LEF1,PPP2R5E,PPP2R1B
Thyroid Cancer Signaling	0.00616595	0.101391139	PPARG,TCF4,KLK3,CDNF,BDNF,NGF,TCF3,CCND1,TCF7,MYC,NTRK3,LEF1,CTNNB1,RXA,TCF7L2
ERK5 Signaling	0.006606934	0.10543869	IL6ST,LIF,YWHAE,SGK1,RPS6KA3,CREB5,NGF,ATF2,EP300,MYC,YWHAQ,FOS,RP56KA6,PTPN11,FOXO3,MEF2C,MAP3K8,RPS6KA5,WNK1,MAP2K5,ELK4
Acute Myeloid Leukemia Signaling	0.009772372	0.149968484	MAP2K6,RUNX1,PIK3C2B,TCF4,AKT2,PIK3C2A,GRB2,PIK3R1,PIK3C2G,NFKB1,T,CF3,CCND1,TCF7,KITLG,MYC,PIM1,PIK3C3,RAFA,CEBPA,LEF1,PIK3CB,JUP,MAP2K5,TCF7L2
Superpathway of Citrulline Metabolism	0.01	0.149968484	NOS1,OTC,GLS,ASS1,OAT,ARG2,NOS2,FYN,PIK3R1,ATF6,NFKB1,PTEN,PPRC,BLK,IKBKB,JUN,PLCE1,CAMK2D,PPP3R1,FOXP3,PLCB1,IRS2,PLCL1,PP3CA,AKT2,ATF3,ITPR2,IKBKE,ITPR1,ATF2,PLCZ1,FOS,PLCB4,CD180,BCL10,VA3Y,SYK,IRS1,SH2B2,NFATC2,PIK3CB,PIK3CA1,MAP2K6,PIK3R1,TAB2,MAP3K5,NFKB1,IKBKB,JUN,MAP3K7,PIK3C3,PPP3R1,TRA5,PP3CA,PIK3C2B,AKT2,PIK3C2A,MITF,MAP3K1,PIK3C2G,IKBKE,TNFRSF11A,XIAP,FOS,MAPK14,CRABP2,ALDH1A2,IGFBP3,NCOA1,TGFB3,PIK3CB,PRKCH,NCOA1,MAP3K5,NFKB1,IKBKB,MAPK14,PIK3C3,PIK3CB,CASP8
PI3K Signaling in B Lymphocytes	0.01023293	0.149968484	MAP2K6,PIK3R1,TAZ2,MAP3K5,NFKB1,IKBKB,JUN,MAP3K7,PIK3C3,PPP3R1,TRA5,PP3CA,PIK3C2B,AKT2,PIK3C2A,MITF,MAP3K1,PIK3C2G,IKBKE,TNFRSF11A,XIAP,FOS,MAPK14,CRABP2,ALDH1A2,IGFBP3,NCOA1,TGFB3,PIK3CB,PRKCH,NCOA1,MAP3K5,NFKB1,IKBKB,MAPK14,PIK3C3,PIK3CB,CASP8
RANK Signaling in Osteoclasts	0.011220185	0.157761127	CHST7,XYLT1,CHSY1,HS2ST1,CHST12,NDST4,CHST15,SULT2A1,DSE,SULT2B1,HS3ST3B1,HS3ST2,CHST11,B3GAT1,HS6ST2,HS3ST1,B3GAT2,HS3ST5
Dermatan Sulfate Biosynthesis	0.011481536	0.157761127	PPARG,ARHGAP22,PIK3C2B,TCF4,AKT2,PIK3C2A,GRB2,PIK3R1,PIK3C2G,NFKB1,T,CF3,CCND1,TCF7,KITLG,MYC,PIM1,PIK3C3,RAFA,CEBPA,LEF1,PIK3CB,JUP,MAP2K5,TCF7L2
PEDF Signaling	0.013803843	0.18238957	BMPR1B,BMP4,MAP3K7,BMP2,SMAD6,BMP7,BMP5,ATF2
Cardiomyocyte Differentiation via BMP Receptors	0.013803843	0.18238957	RDH10,PIK3R1,SMAD3,BMP2,NR2F2,MAP3K5,NFKB1,SMARCA4,PTEN,EP300,NR2F1,JUN,ADCY5,RARA,RARB,CSNK2A1,PRKCE,NTSC1B,BTB16,CITED2,PRKD1,PRKCA,CCNH,AKT2,PRKCQ,RDH14,MED1,MAP3K1,SMAD7,SMAD6,PARP1,KAT2B,FOS,MAPK14,CRABP2,ALDH1A2,IGFBP3,NCOA1,TGFB3,PIK3CB,PRKCH,NCOA1,MAP3K5,NFKB1,IKBKB,MAPK14,PIK3C3,PIK3CB,CASP8
RAR Activation	0.014125375	0.18238957	PRKAB2,PIK3R1,SOCS2,MAP3K5,NFKB1,IKBKB,MAP3K7,PIK3C3,PRKAA2,ACSL4,PRKCE,IRS2,SMPD3,NSMAF,PRKD1,PRKCA,PPARG,PIK3C2B,AKT2,PRKCQ,PIK3C2A,MAP3K1,PIK3C2G,CD36,IKBKE,ACSBG2,SLC2A4,IRS1,SH2B2,PIK3CB,PRKCH,CHENPP7
Type II Diabetes Mellitus Signaling	0.014791084	0.183231442	PTPN13,PIK3R1,NUDT3,NUDT9,NUDT12,IGBP1,STYXL1,PTEN,PTPRC,PIK3C3,PTPN1,MTMR2,PPR1R1C,EYA4,NUDT4,RNGTT,PP3CA,PIK3C2B,PIK3C2A,DUSP27,PIK3C2G,PAWR,PPR2R5A,NUDT15,TNS3,PIP5K1A,SYN1,PTPN11,PPP1R16B,C,DIPT,PPM1H,DUSP23,PPP1R12A,MTMR7,PIK3CB,PPP2R5E,TPTE/TPTE2,PIPK4K2
3-phosphoinositide Biosynthesis	0.015135612	0.1840772	

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Arginine Biosynthesis IV	0.015488166	0.1840772	OTC,ASS1,OAT,GLUD1 PIK3C2B,PRKCQ,PIK3C2A,PIK3R1,SOCS2,RPS6KA3,PIK3C2G,SLC2A4,FOS,RPS6KA1,IRS1,PIK3C3,IGFBP3,CEBPA,IGF1R,PRKCE,PIK3CB,RPS6KA5,PRKCH,PRKCA
Growth Hormone Signaling	0.016595869	0.187931682	CHST7,XYLT1,CHSY1,HS2ST1,CHST12,NDST4,CHST15,SULT2A1,SULT2B1,HS3
Chondroitin Sulfate Biosynthesis	0.016595869	0.187931682	ST3B1,HS3ST2,CHST11,B3GAT1,HS6ST2,HS3ST1,B3GAT2,HS3ST5
Glutamate Receptor Signaling	0.016982437	0.187931682	GRIN2B,GRM3,GRM8,GRID2,GLS,GRIA1,SLC1A1,GRIP1,GRIA4,GNG7,GRIN3A,GNB1,PICK1,GRK4,GRID1,GRK2,GRIA3,GRK1
Gq _i Signaling	0.018197009	0.198152703	RGS18,HTR2B,PIK3R1,DIRAS3,GNB2L1,NFKB1,CHRM3,GNG7,GNB1,IKBKB,HTR2C,RHOB,PPP3R1,PIK3C3,RHOU,PLCB1,PRKCE,PRKD1,PPP3CA,ADRA1B,GNG12,PRKCA,PIK3C2B,AKT2,PRKCQ,PIK3C2A,ITPR2,GRS7,PPR2G,GRS16,IKBKE,I
D-myo-inositol-5-phosphate Metabolism	0.019054607	0.199067334	TPR1,PLD1,ROCK1,PLCB4,NFATC2,PIK3CB,PRKCH,AGTR1 PTPN13,NUDT9,NUDT9,NUDT12,IGBP1,STYXL1,PLCH1,PTEN,PTPRC,PLCE1,PTPN1,PLCB1,MTMR2,PPP1R1C,EYA4,NUDT4,RNGTT,PPP3CA,DUSP27,PAWR,PP2R5A,NUDT15,PLCZ1,PLCB4,TNS3,SYNJ1,PTPN11,PPP1R16B,PPM1H,DUSP23,PPP1R12A,MTMR7,PPP2R5E,TPTE/PTPE2,PIP4K2A
Ephrin Receptor Signaling	0.019498446	0.199067334	RAP1B,FYN,RAPIGEF1,PTPN13,GNB2L1,CXCL12,EPHA4,CREB5,PDGFC,GNG7,E
Dermatan Sulfate Biosynthesis (Late Stages)	0.019498446	0.199067334	P300,GNB1,PTK2,EFNB2,EPHB1,EPHA8,WASL,ACTR3,SORBS1,PROK1,EFNA5,GNG12,IGA4,ITGB1,EPHA7,GRIN2B,AKT2,ANGPT1,KALRN,GRB2,GNAI1,PIK3C2G,EFNA3,VEGFC,EPHA3,EFNA4,FGF1,EFNA1,GRIN3A,ATF2,ROCK1,PTPN11,EPH5,DOCK1,EPHA2
Role of Wnt/GSK-3β Signaling in the Pathogenesis of Influenza	0.022387211	0.226464431	CHST7,HS2ST1,CHST12,NDST4,SULT2A1,CHST15,SULT2B1,DSE,HS3ST3B1,HS3ST2,HS6ST2,CHST11,HS3ST1,HS3ST5
Estrogen-Dependent Breast Cancer Signaling	0.023988329	0.235504928	PIK3C2B,AKT2,HSD17B13,PIK3C2A,PIK3R1,PIK3C2G,NFKB1,CREB5,CCND1,ATF2,EP300,FOS,JUN,PIK3C3,IGF1R,HSD17B12,PIK3CB,HSD17B4,ESR1
TGF-β Signaling	0.024547089	0.239331576	ZFYVE9,MAP2K6,BMP4,GRB2,BMP2,SMAD3,SKI,SMAD6,SMAD7,PTX2,INHBA,EP300,TGFBR2,ZNF423,FOS,BMP1B,MAPK14,TRAF3IP2,MAP3K7,IKBKE,CXCL5,IL6,NFKBIZ,NFKB1,IL7
Epithelial Adherens Junction Signaling	0.02630268	0.247742206	PTPN13,NUDT9,NUDT9,NUDT12,IGBP1,STYXL1,PLCH1,PTEN,PTPRC,PLCE1,ITPKB,PTPN1,PLCB1,MTMR2,PPP1R1C,EYA4,NUDT4,RNGTT,PPP3CA,PIK3C2B,PIK3C2A,DUSP27,PIK3C2G,PAWR,NUDT15,PPP2R5A,PLCZ1,PLCB4,TNS3,PIPK1A,SYNJ1,PTPN11,PPP1R16B,CDIPT,PPM1H,DUSP23,PPP1R12A,MTMR7,PIK3CB,PPP2R5E,TPTE/PTPE2,PIP4K2A
Superpathway of Inositol Phosphate Compounds	0.028183829	0.252348077	IKBKB,FOS,JUN,MAPK14,TRAF3IP2,MAP3K7,IKBKE,CXCL5,IL6,NFKBIZ,NFKB1,IL17A
IL-17A Signaling in Fibroblasts	0.028183829	0.252348077	PIK3C2B,PRKCQ,PIK3C2A,GRB2,PIK3R1,PIK3C2G,MYC,FOS,JUN,PTPN11,PIK3C3,PRKCE,PIK3CB,IRES2,PRKCH,PRKD1,PRKCA
Thrombopoietin Signaling	0.028840315	0.252348077	NOS1,GDNF,GRID2,GRIA1,PIK3R1,GRIA4,PDGFC,GRID1,PROK1,PIK3C3,NEFM,BID,GRK2,PPP3CA,GRK1,PIK3C2B,ACNA1D,PIK3C2A,PIK3C2G,VEGFC,XMAP,GRIN3A,GRK4,CAPN2,PIK3CB,GRK13
Amyotrophic Lateral Sclerosis Signaling	0.028840315	0.252348077	CTGF,PIK3R1,SOCS2,IGFBP7,YWHAQ,PTK2,JUN,PIK3C3,FOXO3,IGF1R,CSNK2A1,IRES2,PIK3C2B,AKT2,PIK3C2A,YWHAE,GRB2,PIK3C2G,IGFBP5,GRB10,FOS,FOXO1,PTPN11,IRES1,IGFBP3,PIK3CB,PRKAR1A
IGF-1 Signaling	0.028840315	0.252348077	BMP4,FST,GRB2,BMP2,SMAD6,SMAD7,NFKB1,PTX2,BMP5,XIAPI,NOG,ATF2,ZNF423,BMPR1B,MAPK14,JUN,MAP3K7,RUNX2,BMP7,BMP6,PRKAR1A
Embryonic Stem Cell Differentiation into Cardiac Lineages	0.029512092	0.252348077	MMP20,PIK3R1,DIRAS3,SMAD3,GNB2L1,WNT16,IL6,CCND1,TCF7,MYC,TGFBR2,GNB1,RHOB,ADCY5,PROK1,GNG12,PIK3C2B,AKT2,IL6R,VEGFC,TCF3,TGFBR2,D3,LEF1,SIAH1,IL6ST2,CFD10,TCF4,PTGER3,FZD1,NFKB1,PDGFC,GNG7,JUN,ARRB1,PIK3C3,DCC,RHOU,CTNNB1,NOS2,PIK3C2A,GRB2,WNT2B,PIK3C2G,FZD8,FO5,WNT8A,FZD4,WNT10A,TLR5,MSH6,PIK3CB,TCF7L2,WNT11,WNT5A,FZD7,PRKAR1A
BMP signaling pathway	0.030902954	0.262421854	PIK3C2B,AKT2,PIK3C2A,SLC2A1,NXPH2,MED1,PIK3R1,PIK3C2G,PFKP,DIO2,DIO3,NRGN,EP300,COL6A3,PIK3C3,NCOA1,ACACA,STRBP,PIK3CB,NCOR2,RXRA,THR,RCAN2,PPARGC1A
Colorectal Cancer Metastasis Signaling	0.032359366	0.264850014	CDKN2A,CCNN1,HDAC4,HDAC8,HDAC2,WEE1,CCNB3,CDK6,E2F3,CCND1,CDKN2B,PPP2R5A,E2F6,CCNE1,CCND2,CCND3,TGFBR3,PPP2R5C,BTRC,PPP2R5E,PPP2R1B,ATR
TR/RXR Activation	0.032359366	0.264850014	MAP2K6,PIK3R1,MAP3K5,CREB5,BCL6,NFKB1,EP300,PTEN,PTPRC,IKBKB,JUN,CAMK2D,MAP3K7,PPP3R1,PIK3C3,PPP3CA,ETS1,PIK3C2B,AKT2,PRKCQ,PIK3C2A,GRB2,MAP3K1,PIK3C2B,IKBKE,TCF3,ATF2,EBF1,MAPK14,SYNJ1,FOXO1,PTPN11,BCL10,VAV3,PAG1,SYK,NFATC2,PIK3CB,PIK3A1,MAP3K8
Cyclins and Cell Cycle Regulation	0.034673685	0.267300641	CHMP6,PRKCQ,CHMP2B,SH3GL3,CHMP4C,PRKCE,SH3GLB1,PRKCH,PDCD6IP,LMN1B1,PRKD1,CHMP3,PRKCA
B Cell Receptor Signaling	0.035481339	0.267300641	CHST7,CHSY1,HS2ST1,CHST12,NDST4,SULT2A1,CHST15,SULT2B1,HS3ST3B1,HS3ST2,HS6ST2,CHST11,HS3ST1,HS3ST5
Mechanisms of Viral Exit from Host Cells	0.035481339	0.267300641	MAP2K6,PIK3C2B,PRKCQ,PIK3C2A,PIK3R1,PIK3C2G,IKBKE,MAP3K5,NFKB1,ATF2,FOS,IKBKB,MAPK14,JUN,MAP3K7,PIK3C3,PRKCE,PIK3CB,PRKCH,PRKD1,PRKCA
Chondroitin Sulfate Biosynthesis (Late Stages)	0.035481339	0.267300641	PTPN13,NUDT3,NUDT9,NUDT9,NUDT12,IGBP1,STYXL1,PTEN,PTPRC,IPMK,PTPN1,MTM2,PPP1R1C,EYA4,NUDT4,RNGTT,PPP3CA,DUSP27,PAWR,PPP2R5A,NUDT15,TNS3,SYNJ1,PTPN11,PPP1R16B,PPM1H,DUSP23,PPP1R12A,MTMR7,PPP2R5E,TPTE/PTPE2
LPS-stimulated MAPK Signaling	0.036307805	0.267300641	PTPN13,NUDT3,NUDT9,NUDT9,NUDT12,IGBP1,STYXL1,PTEN,PTPRC,IPMK,PTPN1,MTM2,PPP1R1C,EYA4,NUDT4,RNGTT,PPP3CA,DUSP27,PAWR,PPP2R5A,NUDT15,TNS3,SYNJ1,PTPN11,PPP1R16B,PPM1H,DUSP23,PPP1R12A,MTMR7,PPP2R5E,TPTE/PTPE2
D-myo-inositol (1,4,5,6)-Tetrakisphosphate Biosynthesis	0.037153523	0.267300641	PTPN13,NUDT3,NUDT9,NUDT9,NUDT12,IGBP1,STYXL1,PTEN,PTPRC,IPMK,PTPN1,MTM2,PPP1R1C,EYA4,NUDT4,RNGTT,PPP3CA,DUSP27,PAWR,PPP2R5A,NUDT15,TNS3,SYNJ1,PTPN11,PPP1R16B,PPM1H,DUSP23,PPP1R12A,MTMR7,PPP2R5E,TPTE/PTPE2
D-myo-inositol (3,4,5,6)-tetrakisphosphate Biosynthesis	0.037153523	0.267300641	ITGB1,AKT2,PRKCQ,GRB2,PIK3R1,CDK5R1,TMEFF2,AREG/AREGB,PTEN,MYC,E
Neuregulin Signaling	0.037153523	0.267300641	RRB2P1,PICK1,PTPN11,NRG1,ERBB4,GRB7,HSP90AA1,PRKCE,ERRFI1,PRKCH,P
Sulfate Activation for Sulfonation	0.03801894	0.270395836	RKD1,PRKCA,ITGA4,PSEN1
			PAPSS1,PAPSS2

Nitric Oxide Signaling in the Cardiovascular System	0.041686938	0.290402265	PIK3C2B,AKT2,CACNA1D,PIK3C2A,GUCY1A3,ITPR2,PIK3R1,FLT1,RYR2,PIK3C2G,VEGFC,ITPR1,PDGFC,PRKG1,PROK1,PIK3C3,KDR,GUCY1A2,HSP90AA1,PIK3CB,PRKAR1A
Dopamine-DARPP32 Feedback in cAMP Signaling	0.042657952	0.290402265	NOS1,KCNJ2,CSNK1A1,CREB5,EP300,PLCE1,DRD1,ADCY5,PPP3R1,PLCB1,PRKCE,PPP2R5C,PLCL1,PRKD1,PPP3CA,PRKCA,PPP1R14C,GRIN2B,CACNA1D,PRKCQ,GUCY1A3,ITPR2,CSNK1G3,GNAI1,KCNJ3,PAWR,ITPR1,PPP2R5A,GRIN3A,ATF2,PLCZ1,PLCB4,PRKG1,CREM,GUCY1A2,PPP1R12A,PRKCH,PPP2R5E,PPP2R1B,PRKAR1A
Notch Signaling	0.043651583	0.290402265	MAML1,MAML2,DLL1,CNTN1,MAML3,RBPJ,PSEN2,HES1,HES7,JAG1,PSEN1,HEY1
P2Y Purigenic Receptor Signaling Pathway	0.043651583	0.290402265	PIK3R1,GNB2L1,NFKB1,CREB5,GNG7,EP300,GNB1,MYC,JUN,PLCE1,ADCY5,PIK3C3,PLCB1,PRKCE,PLCL1,GNG12,PRKD1,PRKCA,PIK3C2B,AKT2,PRKCQ,PIK3C2A,GNAI1,PIK3C2G,ATF2,PLCZ1,FOS,PLCB4,PIK3CB,PRKCH,PRKAR1A
PTEN Signaling	0.043651583	0.290402265	PIK3R1,TGFBR3,NFKB1,CCND1,PTEN,PTK2,TGFBR2,IKBKB,FOXO3,IGF1R,CSNK2A1,ITGA4,ITGB1,AKT2,GRB2,FLT1,PREX2,FGFR2,IKBKE,FOXG1,CNKS3,TNFRSF11A,BMPR1B,MAGI1,FOXO1,SYNJ1,NTRK3,KDR,PIK3CB,MAGI2,BCL2L11
Chronic Myeloid Leukemia Signaling	0.045708819	0.293764965	CDKN2A,PIK3C2B,AKT2,HDAC4,HDAC8,PIK3C2A,HDAC2,GRB2,PIK3R1,SMAD3,PIK3C2G,CDK6,IKBKE,E2F3,NFKB1,CCND1,MECOM,TGFBR2,MYC,IKBKB,E2F6,PTPN11,PIK3C3,TGFBR3,PIK3CB
CD40 Signaling	0.045708819	0.293764965	MAP2K6,PIK3C2B,TRAF3,PIK3C2A,PIK3R1,PIK3C2G,TNFAIP3,IKBKE,NFKB1,FOS,IKBKB,MAPK14,JUN,MAP3K7,PIK3C3,PIK3CB,TRAF5,MAP2K5
NRF2-mediated Oxidative Stress Response	0.045708819	0.293764965	MAP2K6,USP14,PIP1,PIK3R1,NQO2,MAF,DNAJC15,MAP3K5,EP300,CUL3,JUN,MAP3K7,PIK3C3,DNAJC1,PRKCE,FM01,UBE2E3,FKBP5,NFE2L2,PRKD1,PRKCA,GSTA3,PIK3C2B,DNAJB8,PRKCA,PIK3C2A,GSTA4,MAP3K1,DNAJC19,PIK3C2G,BACH1,FOS,MAPK14,MGST2,DNAJC5B,PIK3CB,PRKCH,CDC34,AOX1,DNAJB6,ABC4,ENC1,MAP2K5,DNAJC7
Calcium-induced T Lymphocyte Apoptosis	0.046773514	0.294442163	CD247,PRKCQ,HDAC2,ITPR2,HLA-DRB1,ITPR1,CABIN1,EP300,PPP3R1,NR4A1,PRKCE,NFATC2,CAPN2,PRKCH,PRKD1,PPP3CA,PRKCA
ErbB4 Signaling	0.046773514	0.294442163	PIK3C2B,PRKCQ,PIK3C2A,GRB2,PIK3R1,PIK3C2G,PSEN2,NRG3,ERBB4,PIK3C3,YAP1,PRKCE,PIK3CB,PRKCH,PRKD1,PSEN1,PRKCA
NGF Signaling	0.050118723	0.303389118	RAP1B,PIK3R1,RPS6KA3,MAP3K5,NFKB1,CREB5,NGF,EP300,IKBKB,MAP3K7,PIK3C3,TRAF4,SMPD3,PIK3C2B,AKT2,PIK3C2A,GRB2,MAP3K1,PIK3C2G,IKBKE,ATF2,ROCK1,TRIO,RPS6KA6,PTPN11,MAP3K8,PIK3CB,RPS6KA5
CREB Signaling in Neurons	0.050118723	0.303389118	GRM3,PIK3R1,GRIA1,GRID2,GNB2L1,CREB5,GRIA4,GNG7,EP300,GNB1,PLCE1,CAMK2D,GRID1,ADCY5,PIK3C3,PLCB1,PRKCE,GRK2,PLCL1,PRKD1,GNG12,GRK1,PRKCA,GRIN2B,PIK3C2B,AKT2,PRKCA,PIK3C2A,GRB2,GRM8,ITPR2,GNAI1,PIK3C2G,ITPR1,ATF2,PLCZ1,PLCB4,GRK4,PIK3CB,PRKCH,PRKAR1A,GRIA3
cAMP-mediated signaling	0.050118723	0.303389118	CAMK1D,GRM3,PDE3A,LHCGR,CREB5,CAMK2D,MC1R,ADCY5,PPP3R1,HTR7,PKIA,PDDE11A,OPRM1,PDDE10A,GRM8,PDE4B,CNGA3,ATF2,PDE8A,AKAP13,RAP1G,AP,PKIB,CREM,DUSP4,AGTR1,AKAP12,RGS18,PTGER3,DUSP6,PDE4A,RAPGEF4,CHRM3,EP300,DRD1,CAMK1G,CNGB3,PPP3CA,ADRB2,AKAP5,RGS7,GNAI1,AKAP6,PDE4D,OPRD1,AKAP2/PALM2-
			AKAP2,LPAR1,GLP1R,S1PR1,PDE5A,ADRA2C,AKAP9,PRKAR1A

Supplementary Table 11: All HEPG2 (in house) TCF7L2 Ingenuity Conical pathways with at least nominal $P<0.05$

Ingenuity Canonical Pathways	P-value	B-H Multipole testing correction p-value	Molecules
PPAR α /RXR α Activation	2.40E-06	0.001174898	MAP2K6,NCOA6,TGFB3,MAP4K4,ABCA1,IL1R2,NR2F1,TGFB3,JUN,NFKB1A,HSP90AB1,SOS1,PRKAR1B,PLCB1,NCOR1,PLCL1,GOT2,ACVR1C,ITGB5,PRKCA,ADCY9,ADCY2,GNAS,ACAA1,MED1,ADCY3,ACVR1,PLCG1,NR2C2,IL1R1,TGS1,NCOA3,CAND1,PLCB4,MAPK14,IRS1,PLCG2,TGFB3,IL1B,NCOR2,ADIPOR2,ADCY7,ACVR2A,PRKAR1A
Protein Kinase A Signaling	1.70E-05	0.004168694	MYH10,MYL2,NFATC3,MYLK2,GNB5,TCF7,PTCH2,TGFB3,ROCK2,TH,CA MK2D,PDE7B,PLCB1,CDKN3,PLCL1,EYA2,PRKD1,ADCY9,PTPRD,ADD2,ITPR2,PDE10A,ITPR1,PTPN3,PDE4B,PTPRM,PTP4A1,TTN,CNGA3,PDE8A,E PM2A,PTPRH,MYL12A,PLCG2,ITPR3,TGFB3,LEF1,DUSP4,PTPRA,SIRPA,A KAP12,DUSP6,PTPN14,CDC23,PTPN4,NFKBIA,DUSP10,PTPN1,PRKAR1B,PRKCE,CNGB3,CTNNB1,PRKCA,ADCY2,GNAS,PTPRK,ATF1,MAP3K1,ADCY3,GNAA1,PLCG1,AKAP6,NFATC4,ROCK1,CALM1 (includes others),AKAP2/PALM2-,AKAP2,PLCB4,KDELR3,IHH,NFATC2,PDE5A,CNGB1,ADCY7,PTPRT,PTPN2,TCF7L2,PRKAR1A
Wnt/ β -catenin Signaling	5.12861E-05	0.008317638	FRZB,PPP2R2A,SOX10,TGFB3,SOX12,CSNK1A1,TLE1,WNT6,KREMEIN1,CCND1,TCF7,MYC,TGFB3,SOX2,SOX9,JUN,DKK2,SOX18,CTNNB1,ACVR1C,SOX4,SRC,AKT2,AXIN2,LRP5,GJA1,WNT9B,ACVR1,SOX11,CDH2,WNT8A,CDH5,GNAA1,TLE3,TGFB3,LEF1,FZD5,DKK1,ACVR2A,LRP1,TCF7L2,TRIM24,BMP2,NR2F2,SMARDC2,MAP3K5,VEGFA,NR2F1,JUN,ALDH1A1,ALDH1A3,PRKAR1B,PRKCE,NCOR1,SORBS3,NTSC1B,SMAD1,CITED2,PRKD1,PRKCA,ADCY9,SRC,ADCY2,AKT2,GNAS,MED1,MAP3K1,ADCY3,SMAD7,PIK3R3,MAPK14,TAFA4,IGFBP3,NCOA1,TGFB3,PIK3CB,NCOR2,NRIP1,ADCY7,SCAND1,PRKAR1A,ADH4
RAR Activation	6.91831E-05	0.008317638	NODAL,BMP4,MYL2,BMP2,TGFB3,TCF7,TGFB3,PRKCE,CTNNB1,ACVR1C,SMAD1,PRKD1,PRKCA,LRP5,ACVR1,MAPK14,TGFB3,FZD5,LEF1,BMP7,DKK1,BMP6,TCF7L2,ACVR2A,LRP1
Factors Promoting Cardiogenesis in Vertebrates	0.000104713	0.01023293	MAP2K6,GNB5,CSNK1A1,CABIN1,TGFB3,CAMK2D,SOS1,PRKAR1B,IGF1R,PLCB1,PRKCE,PLCL1,PRKD1,PRKCA,ADCY9,PIK3C2B,SRC,ADCY2,AKT2,HDAC4,GNAS,ITPR2,ADCY3,MAP2K1,GNAA1,SLC8A3,MEF2A,PLCG1,NFA TC4,ITPR1,PIK3R3,CALM1 (includes others),PLCB4,MAPK14,PLCG2,ITPR3,TGFB3,PIK3CB,SLC8A1,ADCY7,PRKAR1A
Role of NFAT in Cardiac Hypertrophy	0.000177828	0.014454398	GLI2,POMC,PTCH2,VEGFA,JUN,PRKAR1B,PRKCE,NOS2,PRKD1,PRKCA,ADCY9,ADCY2,GNAS,ITPR2,ADCY3,GNAA1,CRH,MEF2A,PLCG1,ITPR1,CALM1 (includes others),MAPK14,PLCG2,GNAA1,ITPR3,GNR4A1,ADCY7,PRKAR1A
Corticotropin Releasing Hormone Signaling	0.000346737	0.022908677	GRIN2A,GRIA1,TACR1,CAMK2D,PRKAR1B,PRKCE,PLCB1,KCNQ3,PLCL1,PRKD1,PRKCA,SRC,PIK3C2B,GRM8,ITPR2,GRIA2,PLCG1,ITPR1,GRM7,PIK3R3,PLCB4,KCNQ2,PLCG2,ITPR3,PIK3CB,PRKAR1A
Neuropathic Pain Signaling In Dorsal Horn Neurons	0.000380189	0.022908677	DPY2,BMP4,GLI2,MYL2,NFATC3,GNB5,CXCL12,LIMK2,WNT6,PTCH2,NCK2,VEGFA,ROCK2,CFL2,UNC5D,PLCB1,ADAM23,PLXB2,PLCL1,PRKD1,PIK3C2B,ACTR2,PAPP,AKT2,KALRN,TUBB2A,MMP2,HHIP,PIK3R3,A DAM18,MYL12A,ADAM12,PLCG2,SEMA6D,GNAA1,RTN4,FZD5,LEF1,ADA M29,EPHA2,MMP21,SLT1,BMP2,SEMA6A,EPHA4,PDGF,ABLIM1,ACTR3,EFNA5,SOS1,PRKAR1B,ADAM19,PRKCE,SEMA3B,ROBO2,SEMA3F,PRKCA,TUBB1,GNAS,NRP2,WNT9B,GNAA12,C9orf3,GNAA1,PLCG1,NFATC4,EPHA3,ITGA3,EFNA1,ROCK1,WNT8A,PLCG4,WIFP1,NFATC2,PIK3CB,BMP7,BMP6,PRKAR1A,SEMA7A
Axonal Guidance Signaling	0.000489779	0.026915348	PRODH,GLS,ASS1,ARG2,NOS2,CPS1,ARG1
Superpathway of Citrulline Metabolism	0.001023293	0.050118723	JUN,SOS1,PRKAR1B,PRKCE,PRKD1,AGT,PRKCA,ADCY9,PIK3C2B,ADCY2,GNAS,ITPR2,ADCY3,MAP3K1,REN,PLCG1,ITPR1,PIK3R3,MAPK14,PLCG2,ITPR3,PAK7,PIK3CB,ADCY7,AGTR1,PRKAR1A
Renin-Angiotensin Signaling	0.001548817	0.063095734	HAL,MTHFD2A,AMHDH1,MTHFD2L,MTHFD1L
Histidine Degradation III	0.001584893	0.063095734	ACSL3,ACSS3,ALDH1A1,ALDH1A3,ALDH3A2,ALDH3A1,ACSL1
Oxidative Ethanol Degradation III	0.001698244	0.063095734	SRC,PIK3C2B,AKT2,JAK1,ITPR2,MAP3K1,SRF,PLCG1,ITPR1,PIK3R3,JUN,MAPK14,SOS1,ITPR3,PIK3CB,PRKCA
EGF Signaling	0.001905461	0.063095734	MYH10,MYL2,TGFB3,PVRL3,MLLT4,TCF7,TGFB3,CTNN2,ACTR3,SORBS1,PVRL1,CTNNB1,ACVR1C,SRC,ACTR2,TUBB1,AKT2,FGFR1,TUBB2A,SNA1,ACVR1,PTPRM,FGF1,CDH2,MAGI1,MYH9,LEF1,PARD3,ACVR2A,TCF7L2,CTNN1
Epithelial Adherens Junction Signaling	0.001995262	0.063095734	CCND1,ARNT,NR2F1,TGM2,MYC,ALDH1A1,JUN,HSP90AB1,ALDH1A3,ALD3A2,ALDI3A1,NFE2L2,ALDH5A1,AHR,SRC,NFIC,MED1,GSTA4,NQO1,CDK6,NCOA3,MGST2,NFIA,TGFB3,IL1B,NFIB,NRIP1,NCOR2,DCT,ESR1
Aryl Hydrocarbon Receptor Signaling	0.002137962	0.063095734	BMP4,JAK1,TAB2,CCND1,PTCH2,MYC,TGFB3,E2F6,CTNN2A,CAMK2D,RHO,PLCB1,SMAD1,PRKD1,CASP10,ADCY9,PIK3C2B,AKT2,ARHGEF4,CDK6,PIK3R3,BCL2L1,MAX,ARHGEF16,RS1,GNAA1,TGFB3,PAK7,LEF1,FZD5,MAP2K6,BMP2,HIF1A,MAP3K5,NFKBIA,JUN,SOS1,PRKAR1B,PRKCE,BID,CTNNB1,CASP8,PRKCA,SRC,LRP5,ADCY2,GNAS,GNAA12,ADCY3,GNAA1,S MAD7,PLCB4,MAPK14,RASGRF1,IHH,BMP7,PIK3CB,BMP6,ADCY7,LRP1,PRKAR1A,PSEN1,CTNND1
Molecular Mechanisms of Cancer	0.002290868	0.063095734	MYL2,MAP3K5,F2,CDH11,ROCK2,JUN,NFKBIA,CDH16,CTNNB1,PIK3C2B,SRC,AKT2,CDH4,GNA12,MAP3K1,CDH6,MEF2A,ROCK1,PIK3R3,CDH2,MYL12A,CDH9,CDH5,CDH20,VAV3,CDH8,PIK3CB
Gα12/13 Signaling	0.002454709	0.063095734	LIPC,GCLC,CES2,CHST15,ARNT,HS6ST1,ALDH1A1,CAMK2D,NR112,SUMO1,ALDH3A2,HS6ST3,ALDH3A1,PRKD1,AHR,PIK3C2B,HDAC4,MED1,UGT1A1,PIK3R3,HS3ST3B1,NCOA1,HS3ST5,MAP2K6,GAL3T2,PPP2R2A,MAP3K5,CUL3,HSP90AB1,ALDH1A3,PRKCE,SMOX,NOS2,NFE2L2,ALDH5A1,CITE2,PRKCA,GSTA4,MGNT1,NQO1,MAP3K1,SULT2B1,MAPK14,MGST2,HS3S2,IL1B,PIK3CB,NRIP1,NCOR2,SCAND1,UGT1A9 (includes others)
Xenobiotic Metabolism Signaling	0.002511886	0.063095734	

Growth Hormone Signaling	0.002630268	0.063095734	PIK3C2B,SOCS1,SOCS2,SRF,PLCG1,ONECUT1,PIK3R3,IRS1,PLCG2,IGF1R,IGFBP3,PRKCE,PIK3CB,RPS6KA2,SOCS5,A2M,PRKD1,PRKCA
Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	0.002951209	0.069183097	SOCS1,TRAF3,NFATC3,CXCL12,CNSK1A1,WNT6,CCND1,TCF7,MYC,IL1R2,VEGFA,ROCK2,CAMK2D,TRAF3IP2,DKK2,PLCB1,PLCL1,PRKD1,PIK3C2B,AKT2,SELE,PIK3R3,PLCG2,GNAO1,LEF1,FZD5,MAP2K6,FN1,FRZB,PDGFC,NFKBIA,JUN,PRKCE,CTNNB1,NOS2,PRKCA,SRC,LRP5,WNT9B,DAAM1,PLCG1,CEPB,NFATC4,IL1R1,ROCK1,CALM1 (includes others),WNT8A,PLCB4,MAPK14,NFATC2,IL1B,PIK3CB,DKK1,TCF7L2,LRP1
Cellular Effects of Sildenafil (Viagra)	0.003235937	0.072443596	MYH10,MYH6,MYL2,SLC4A11,PRKAR1B,PLCB1,KCNQ3,PLCL1,ADCY9,SLC4A5,ADCY2,GNAS,ITPR2,ADCY3,PLCG1,PDE4B,ITPR1,CALM1 (includes others),PLCB4,MYL12A,KCNQ2,PLCG2,ITPR3,MYH9,DE5A,ADCY7,PRKAR1A,SLC4A10
Urea Cycle	0.003715352	0.072443596	ASS1,ARG2,CPS1,ARG1
Ethanol Degradation II	0.003890451	0.072443596	ACSL3,ACSS3,ALDH1A1,ALDH1A3,ALDH3A2,ALDH3A1,ACSL1,ADH4,DHRS4
Endothelin-1 Signaling	0.003981072	0.072443596	MYC,JUN,EDN1,PLB1,SOS1,PLCB1,PRKCE,CASP8,NOS2,PLCL1,PRKD1,CASP10,PRKCA,ADCY9,SRC,PIK3C2B,ADCY2,GNAS,ITPR2,GNA12,ADCY3,GNA11,PLCG1,PLA2G2E,ITPR1,PIK3R3,PLA2G4A,PLA2G6,PLCB4,MAPK14,PLCG2,GNAO1,ITPR3,PIK3CB,ADCY7
Ethanol Degradation IV	0.004073803	0.072443596	ACSL3,ACSS3,ALDH1A1,ALDH1A3,ALDH3A2,ALDH3A1,ACSL1
CXCR4 Signaling	0.004365158	0.072443596	MYL2,CD4,CXCL12,GNB5,ROCK2,JUN,RHOB,PLCB1,PRKCE,PRKD1,PRKC,ADCY9,PIK3C2B,SRC,ADCY2,AKT2,GNAS,ITPR2,GNA12,ADCY3,GNA11,ITPR1,PIK3R3,ROCK1,MYL12A,PLCB4,GNAO1,ITPR3,PIK3CB,PAK7,ELMO1,ADCY7
CREB Signaling in Neurons	0.004365158	0.072443596	GRIN2A,GRIA1,GNB5,CAMK2D,SOS1,PRKAR1B,PRKCE,PLCB1,PLCL1,PRKD1,PRKCA,ADCY9,PIK3C2B,ADCY2,AKT2,GNAS,GRM8,ITPR2,GNA12,ADCY3,GRIA2,GNA11,PLCG1,ITPR1,GRM7,PIK3R3,CALM1 (includes others),PLCB4,GRK4,PLCG2,GNAO1,ITPR3,PIK3CB,ADCY7,PRKAR1A
Transcriptional Regulatory Network in Embryonic Stem Cells	0.004365158	0.072443596	SOX2,ISL1,TRIM24,CDYL,MYF5,MEIS1,OTX1,HOXB1,HNF4A,FOXC1,ONECUT1,ZFHX3
Human Embryonic Stem Cell Pluripotency	0.004677351	0.075857758	NODAL,BMP4,BMP2,WNT6,PDGFC,TCF7,SOX2,TGFBR2,CTNNB1,SMAD1,PDGFRB,PIK3C2B,AKT2,GNAS,WNT9B,FGFR1,SMAD7,ACVR1,PIK3R3,WN8A,TGFBR3,S1PR1,BMP7,PIK3CB,LEF1,FZD5,BMP6,TGF7L2,SALL4
Melatonin Signaling	0.005370318	0.085113804	MAP2K6,GNAI1,PLCG1,MTNR1B,CALM1 (includes others),PLCB4,CAMK2D,RORA,PLCG2,GNAO1,PRKAR1B,PLCB1,PRKCE,P,LCL1,PRKD1,PRKAR1A,PRKCA
RhoGDI Signaling	0.005754399	0.089125094	MYL2,PIKFYVE,GNB5,LIMK2,CDH11,ROCK2,ACTR3,CFL2,RHOB,ARHGAP12,CDH16, DLC1, PRKCA, ACTR2, SRC, ARHGEF4, GNAS, CDH4, GNA12, CDH16, GNA11, ITGA3, ROCK1, ARHGAP5, MYL12A, CDH2, CDH9, CDH5, CDH20, ARHGAP16, GNAO1, CDH8, PAK7, ARHGDI, ESR1
eNOS Signaling	0.006456542	0.09332543	PDGFC,VEGFA,HSP90AB1,PRKAR1B,CNGB3,CASP8,ADCY9,AQP7,PIK3C2B,AKT2,ADCY2,GNAS,ITPR2,ADCY3,PLCG1,ITPR1,CNGA3,PIK3R3,CALM1 (includes others),PLCG2,ITPR3,CHRNE,CNGB1,PIK3CB,ADCY7,ESR1,PRKAR1A
α -Adrenergic Signaling	0.00676083	0.095499259	ADCY9,ADCY2,GNAS,ITPR2,ADCY3,SLC8A3,GNB5,GNA11,PLCG1,ITPR1,CALM1 (includes others),PLCG2,ITPR3,PRKAR1B,PRKCE,SLC8A1,ADCY7,PRKD1,PRKAR1A,PRKCA
Neuregulin Signaling	0.007585776	0.106414302	SRC,AKT2,PLCG1,ITGA3,TMEFF2,MYC,PIK3R3,ERBB2IP,HSP90AB1,NRG3,PLCG2,ERBB4,GRB7,SOS1,TGFA,DLG4,PRKCE,PRKD1,PSEN1,PRKCA
Gap Junction Signaling	0.009549926	0.129717927	CSNK1A1,SP3,SOS1,PRKAR1B,PRKCE,PLCB1,PLCL1,CTNNB1,PRKD1,PRKCA,ADCY9,SRC,PIK3C2B,TUBB1,AKT2,ADCY2,GNAS,ITPR2,ADCY3,TUBB2A,GNAI1,PLCG1,ITPR1,DRD2,PIK3R3,PLCB4,PLCG2,ITPR3,PIK3CB,ADCY7,PRKAR1A
TGF- β Signaling	0.010964782	0.134276496	MAP2K6,NODAL,BMP4,BMP2,ACVR1,SMAD7,INHBB,TGIF1,TGFBR2,ZNF423,JUN,MAPK14,SOS1,TGFB3,BMP7,HNF4A,SMAD1,ACVR1C,ACVR2A
Virus Entry via Endocytic Pathways	0.011220185	0.134276496	PIK3C2B,SRC,ITSN1,CLTC,ITGA6,PLCG1,ITGA3,ITGA1,PIK3R3,AP1G2,PLC G2,PRKCE,PIK3CB,ITGA1,ITGB4,ITGB6,CXADR,ITGB5,PRKD1,PRKCA
Hepatic Fibrosis / Hepatic Stellate Cell Activation	0.012022644	0.134276496	MYH10,MYH6,FN1,MYL2,PDGFC,IL1R2,VEGFA,TGFBR2,EDN1,IGF1R,PDGFR,AGT,FGFR1,SMAD7,IFNNGR1,MMP2,IL1R1,FGF1,CD40,TGFA,IGFBP3,TGF8,IL1B,MYH9,A2M,AGTR1,CCR7,COL3A1
Regulation of IL-2 Expression in Activated and Anergic T Lymphocytes	0.012022644	0.134276496	NFATC3,MAP3K1,PLCG1,TOB1,NFATC4,TGFBR2,CD28,CALM1 (includes others),NFKBIA,JUN,BCL10,VAV3,PLCG2,SOS1,LAT,TGFB3,NFATC2,CARD11
CCR3 Signaling in Eosinophils	0.012022644	0.134276496	PIK3C2B,GNAS,ITPR2,GNAI1,GNB5,LIMK2,PLA2G2E,ITPR1,PIK3R3,ROCK2,ROCK1,CALM1 (includes others),PLA2G6,PLA2G4A,PLCB4,MAPK14,CFL2,ITPR3,PLCB1,PRKCE,PAK7,PIK3CB,PRKD1,PRKCA
Melanocyte Development and Pigmentation Signaling	0.012302688	0.134276496	ADCY9,PIK3C2B,SRC,ADCY2,GNAS,SOX10,ADCY3,PLCG1,POMC,PIK3R3,MC1R,PLCG2,SOS1,PRKAR1B,PIK3CB,DCT,RPS6KA2,ADCY7,PRKAR1A
Thrombin Signaling	0.012589254	0.134276496	MYL2,GNB5,F2,ROCK2,CAMK2D,RHOB,SOS1,PRKCE,PLCB1,PLCL1,PRKD1,PRKCA,ADCY9,SRC,PIK3C2B,ARHGEF4,ADCY2,AKT2,GNAS,ITPR2,GNA12,ADCY3,GNA11,PLCG1,ITPR1,ROCK1,PIK3R3,MYL12A,PLCB4,MAPK14,PLCG2,PRKAR1B,PLCB1,PIK3CB,PLCL1,ADCY7,PRKAR1A
T Cell Receptor Signaling	0.012882496	0.134276496	PIK3C2B,NFATC3,CD4,MAP3K1,PLCG1,NFATC4,CD8A,PIK3R3,CD28,SHB, CALM1 (includes others),PTPRH,JUN,NFKBIA,BCL10,VAV3,SOS1,LAT,NFATC2,PIK3CB,CAR D11
Putrescine Degradation III	0.013182567	0.134276496	ALDH1A1,ALDH1A3,ALDH3A2,SAT1,SMOX,ALDH3A1
Prolactin Signaling	0.013182567	0.134276496	SOCS1,PIK3C2B,SOCS2,PLCG1,CEBPB,TCF7,MYC,PIK3R3,JUN,IRS1,PLC G2,SOS1,PRKCE,PIK3CB,SOCS5,PRKD1,PRKCA
Leptin Signaling in Obesity	0.013182567	0.134276496	ADCY9,PIK3C2B,ADCY2,AKT2,GNAS,GNA12,ADCY3,GNA11,PLCG1,PDGFC,PIK3R3,PLCB4,RHOB,PLCG2,S1PR1,PLCB1,PIK3CB,CASP8,PLCL1,ADCY7,SMPD3,PDGFRB,CASP10
Sphingosine-1-phosphate Signaling	0.013182567	0.134276496	PRODH,GLS,ARG2,ARG1
Citrulline Biosynthesis	0.013803843	0.136144468	HNMT,ALDH1A1,ALDH1A3,ALDH3A2,ALDH3A1
Histamine Degradation	0.014454398	0.138675583	PIK3C2B,AKT2,NFATC3,ITPR2,CD4,HLA-DQA1,PLCG1,ITPR1,NFATC4,PLEKHA3,INPP5D,PIK3R3,CALM1 (includes others)
iCOS-iCOSL Signaling in T Helper Cells	0.014791084	0.139958732	

Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis	0.016595869	0.151705037	others),ICOS,CD28,CAMK2D,NFKBIA,CD40,LAT,ITPR3,NFATC2,PIK3CB MAP2K6,BMP4,FRZB,NFATC3,BMP2,TAB2,CSNK1A1,WNT6,MAP3K5,TCF7, IL1R2,NFKBIA,JUN,DKK2,CTNNB1,ALPL,SMAD1,SRC,PIK3C2B,LRP5,AKT2, WNT9B,DLX5,NFATC4,IL1R1,ITGA3,PIK3R3,CALM1 (includes others),WNT8A,MAPK14,NFATC2,IL1B,PIK3CB,FZD5,LEF1,BMP7,DKK1,BM P6,LRP1,TCF7L2			
PI3K Signaling in B Lymphocytes	0.018197009	0.151705037	BLNK,AKT2,ATF1,NFATC3,ITPR2,PLCG1,ITPR1,NFATC4,PLEKHA3,INPP5D ,CALM1 (includes others),PLCB4,JUN,CAMK2D,NFKBIA,CD40,BCL10,IRS1,PLCG2,VAV3,ITPR 3,NFATC2,PLCB1,PIK3CB,PLCL1			
γ -linolenate Biosynthesis II (Animals)	0.018197009	0.151705037	ACSL3,ACSL6,ACSL5,CYB5A,ACSBG2,ACSL1			
Tetrahydrofolate Salvage from 5,10-methenyltetrahydrofolate	0.018620871	0.151705037	MTHFD2,MTHFD2L,MTHFD1L			
Acetate Conversion to Acetyl-CoA	0.018620871	0.151705037	ACSL3,ACSS3,ACSL1 BLNK,NFATC3,CD4,HLA-DQA1,GNB5,CSNK1A1,CABIN1,CD28,JUN,NFKBIA,SOS1,XPO1,PLCB1,PIK 3C2B,AKT2,GNAS,ITPR2,GNAA1,GNAA1,MEF2A,PLCG1,ITPR1,NFATC4,PIK 3R3,CALM1 (includes others),PLCB4,PLCG2,GNAA1,LAT,ITPR3,NFATC2,PIK3CB PIK3C2B,AKT2,CDK6,PLCG1,MMP2,MAP3K5,CCND1,PIK3R3,SOS1,PRKCE ,PIK3CB,ITGB4,PARD3,ITGB6,ITGB5,PRKD1,PRKCA			
Role of NFAT in Regulation of the Immune Response	0.019054607	0.151705037	 MYC,MAX,PSMF1,SAT1,PSME4,PSMB11,CTNNB1 ROCK2,ROCK1,PIK3R3,PIK3C2B,CFL2,EFNA5,VAV3,PIK3CB,EPHA4,EPHA 3,EPHA2,EFNA1 PIK3C2B,AKT2,RBL2,CDK6,PLCG1,PDGFC,CCND1,IGF2R,PIK3R3,E2F6,CA LM1 (includes others),CAMK2D,PLCG2,SOS1,IGF1R,PRKCE,PIK3CB,PRKD1,PRKCA,PDG FRB			
HER-2 Signaling in Breast Cancer	0.019498446	0.151705037	 MAP2K6,EIF2B4,MYL2,GNB5,SRF,MAP3K5,ROCK2,TGFB2,JUN,RHOB,SO S1,IGF1R,PRKAR1B,PLCB1,PLCL1,ADCY9,PIK3C2B,ADCY2,GNAS,GNAA12, ADCY3,MAP3K1,MEF2A,GNAA1,PLCG1,NFATC4,ROCK1,PIK3R3,CALM1 (includes others),MYL12A,PLCB4,MAPK14,IRS1,PLCG2,GNAA1,TGFB3,ADRA2C,PIK3 CB,ADCY7,PRKAR1A			
Polyamine Regulation in Colon Cancer	0.019498446	0.151705037	ACSL3,ACSL6,ACSL5,ACSBG2,ACSL1 PPP2R2A,GRIA1,PLB1,IGF1R,PRKCE,PLCB1,NOS2,PLCL1,PRKD1,PRKCA, GNAS,GRM8,ITPR2,GNAA12,GNAA1,CRH,GRIA2,PLCG1,PLA2G2E,ITPR1,GR M8,PLA2G6,PLA2G4A,PLCB4,PLCG2,GNAA1,ITPR3			
Ephrin A Signaling	0.019952623	0.151705037	Synaptic Long Term Depression	0.020892961	0.151705037	MAP2K6,MYH10,MYH6,FN1,MYL2,PPP2R2A,BMP2,HIF1A,CCND1,PDGFC,N CK2,MYC,VEGFA,JUN,RHOB,CFL2,PPAP2B,ITGB4,CTNNB1,NOS2,DSP,IT GB5,PIK3C2B,AKT2,TMSB10/TMSB4X,FERMT2,SNAI1,PIK3R3,LIMS1,IRS1, MYH9,PIK3CB,LEF1,ITGB6 PIK3C2B,SRC,JAK1,MAP3K1,SRF,PLCG1,PDGFC,INPP5D,MYC,PIK3R3,SY NJ2,JUN,PLCG2,SOS1,PIK3CB,PRKCA,PDGFRB
Glioma Signaling	0.020417379	0.151705037	ILK Signaling	0.021379621	0.151705037	ACTR2,PIK3C2B,AKT2,NFATC3,ITPR2,CD4,MAP3K1,HLA-DQA1,PLCG1,ITPR1,NFATC4, PIK3R3,CALM1 (includes others),CD28,JUN,ACTR3,NFKBIA,BCL10,LAT,ITPR3,NFATC2,PIK3CB,CAR D11 PIK3C2B,SOCS1,AKT2,ACSL3,SOCS2,MAP3K1,ACSL6,MAP3K5,CEBPB,AC SBG2,PIK3R3,NFKBIA,IRS1,ACSL5,PRKCE,PIK3CB,ADIPOR2,SOCS5,ENP P7,SMPD3,ACSL1,PRKD1,PRKCA
Cardiac Hypertrophy Signaling	0.020417379	0.151705037	PDGF Signaling	0.021877616	0.151705037	ACTR2,PIK3C2B,AKT2,NFATC3,ITPR2,CD4,MAP3K1,HLA-DQA1,PLCG1,ITPR1,NFATC4, PIK3R3,CALM1 (includes others),CD28,JUN,ACTR3,NFKBIA,ITPR3,PLCB1,PRKCE,NFATC2,PIK3CB,PR K1,PRKCA
Fatty Acid Activation	0.020892961	0.151705037	CD28 Signaling in T Helper Cells	0.022387211	0.151705037	EIF2S2,PIK3C2B,SRC,AKT2,EIF2B4,EIF1,PLCG1,HIF1A,PDGFC,ARNT,ROC K1,VEGFA,PIK3R3,ROCK2,BCL2L1,PLCG2,SOS1,PIK3CB,PRKCA MAP2K6,SRC,ITPR2,GNAA12,MEF2A,SRF,EPHA4,ITPR1,ROCK2,ROCK1,PL CB4,MAPK14,JUN,RHOB,SOS1,ITPR3,PLCB1,PRKCE,IL1B,PRKD1,PRKCA PIK3C2B,ID2,AKT2,JAK1,BMP4,TCF7,MYC,PIK3R3,SOX2,ID1,MAPK14,SOS 1,PIK3CB,FZD5,LEF1,CTNNB1,SMAD1,TCF7L2,ID4,ZFP42
			Inhibition of Matrix Metalloproteases	0.0222908677	0.152405275	MMP21,MMP20,SDC1,HSPG2,ADAM12,THBS2,MMP2,A2M,MMP17,LRP1 MMP20,SPN,NOX3,CTNNA3,CXCL12,MLLT4,RAPGEF4,ROCK2,CTNNA2A RHGAP12,PRKCE,CTNNB1,DLC1,PRKD1,MMP17,PRKCA,PIK3C2B,SRC,G NA1,PLCG1,MMP2,ITGA3,ITGA6,ROCK1,ARHGAP5,PIK3R3,WIFP1,MAPK1 4,ITGAM,CDH5,VAV3,PLCG2,PECAM1,PIK3CB,CTNND1
			Leukocyte Extravasation Signaling	0.023988329	0.156675107	AKAP12,DUSP6,LHCGR,RAPGEF4,CAMK2D,PDE7B,MC1R,FSHR,PRKAR1 B,CNGB3,ADCY9,ADORA3,SRC,ADCY2,GNAS,OPRM1,PDE10A,GRM8,ADC Y3,GNAA1,AKAP6,PDE4B,DRD2,MC4R,CNGA3,PDE8A,GRM7,CALM1 (includes others),AKAP2/PALM2- AKAP2,GLP1R,GNAA1,S1P1R,PDE5A,DUSP4,CNGB1,ADRA2C,ADCY7,AG TR1,PRKAR1A
cAMP-mediated signaling	0.024547089	0.156675107	Glioblastoma Multiforme Signaling	0.024547089	0.156675107	WNT6,CCND1,PDGFC,MYC,E2F6,RHOB,SOS1,IGF1R,PLCB1,CTNNB1,PLC L1,PDGFRB,SRC,PIK3C2B,AKT2,WNT9B,ITPR2,CDK6,PLCG1,ITPR1,PIK3R 3,PLCG2,WNT8A,PLCG2,ITPR3,PIK3CB,FZD5,LEF1
			GNRH Signaling	0.02630268	0.164058977	MAP2K6,MAP3K5,CAMK2D,JUN,SOS1,PRKAR1B,PRKCE,PLCB1,PRKD1,P RKCA,ADCY9,SRC,ADCY2,GNAS,ITPR2,MAP3K1,ADCY3,GNAA1,ITPR1,PLC B4,MAPK14,ITPR3,PAK7,ADCY7,PRKAR1A
			TR/RXR Activation	0.027542287	0.170608239	PIK3C2B,AKT2,NCOA6,SLC2A1,TRH,MED1,HIF1A,DIO2,DIO3,NCOA3,PIK 3R3,KLF9,NCOA1,PIK3CB,SYT2,NCOR1,NCOR2,THRB
			Ephrin Receptor Signaling	0.028183829	0.170608239	GRIN2A,ITSN1,GNB5,CXCL12,LIMK2,MAP4K4,EPHA4,PDGFC,ROCK2,VEG FA,NCK2,ACTR3,CFL2,SORBS1,EFNA5,SOS1,SRC,ACTR2,AKT2,GNAS,KA LRN,GNAA12,GNAA1,EPHA3,ITGA3,FGF1,EFNA1,ROCK1,WIFP1,GNAA1,PAK 7,EPHA2
			Glutamate Receptor Signaling	0.028840315	0.170608239	GRIN2A,SLC1A4,GRM8,GLS,GRIA1,SLC17A2,SLC1A3,GRIA2,GRM7,CALM1 (includes others),GRIK4,SLC1A2,DLG4
			Leukotriene Biosynthesis	0.028840315	0.170608239	GGTL1C1,DPEP1,MGST2,GGT1,GGT7
			γ -glutamyl Cycle	0.028840315	0.170608239	GGTL1C1,GCLC,GGT1,A2LD1,GGT7
			Role of Oct4 in Mammalian Embryonic	0.029512092	0.173780083	SOX2,NR2F1,FOXA1,FOXA2,NR2F2,JARID2,TDRD7,MEF2A,SH3GLB1,HOX

Stem Cell Pluripotency		B1,SALL4
Chemokine Signaling	0.030199517	0.174984669 SRC,MYL2,CXCL12,GNAI1,PLCG1,LIMK2,ROCK2,CALM1 (includes others),PLCB4,CAMK2D,JUN,MAPK14,PLCG2,PLCB1,PRKCA
P2Y Purigenic Receptor Signaling Pathway	0.035481339	ADCY9,PIK3C2B,AKT2,ADCY2,GNAS,ADCY3,GNB5,GNAI1,PLCG1,MYC,PIK3R3,PLCB4,JUN,PLCG2,PRKAR1B,PLCB1,PRKCE,PIK3CB,PLCL1,ADCY7,P
Calcium-induced T Lymphocyte Apoptosis	0.037153523	RKD1,PRKAR1A,PRKCA ITPR2,CD4,HLA-DQA1,PLCG1,ITPR1,CBIN1,CALM1 (includes others),ITPR3,NR4A1,PRKCE,NFATC2,PRKD1,PRKCA
ErbB4 Signaling	0.037153523	PIK3C2B,PLCG1,PIK3R3,NRG3,PLCG2,ERBB4,SOS1,YAP1,PRKCE,PIK3CB,PRKD1,PSEN1,PRKCA
Basal Cell Carcinoma Signaling	0.03801894	BMP4,GLI2,WNT9B,BMP2,WNT6,HHIP,TCF7,PTCH2,WNT8A,LEF1,FZD5,BM
CDP-diacylglycerol Biosynthesis I	0.038904514	P7,BMP6,CTNNB1,TCF7L2 AGPAT4,GPAM,LCLAT1,MBOAT2,AGPAT3
Aldosterone Signaling in Epithelial Cells	0.039810717	SGK1,PIKFYVE,DNAJC10,HSP90AB1,SOS1,PRKCE,PLCB1,DNAJB1,PLCL1,SCNN1B,PRKD1,PRKCA,AHCY,PIK3C2B,DNAJB12,ITPR2,DNAJB3,PLCG1,I TPR1,PIK3R3,ODF1,NEDD4,PLCB4,SCNN1G,PLCG2,ITPR3,PIK3CB,DNAJB6
Role of Tissue Factor in Cancer	0.039810717	PIK3C2B,SRC,AKT2,GNA12,ITGA6,LIMK2,ITGA3,FRK,F2,PIK3R3,VEGFA,B CL2L1,MAPK14,CFL2,PLCB1,IL1B,FGF,PIK3CB,RPS6KA2,ITGB5,PRKCA
Non-Small Cell Lung Cancer Signaling	0.042657952	PIK3R3,PIK3C2B,AKT2,FHIT,ITPR2,SOS1,ITPR3,TGFA,CDK6,PLCG1,PIK3C B,ITPR1,CCND1,PRKCA
PEDF Signaling	0.042657952	PIK3C2B,AKT2,GDNF,SRF,ZEB1,TCF7,PIK3R3,ROCK2,ROCK1,BCL2L1,MA PK14,NFKBIA,SOD2,PIK3CB,CASP8
PPAR Signaling	0.046773514	MED1,MAP4K4,IL1R1,PDGFC,IL1R2,NR2F1,NFKBIA,JUN,HSP90AB1,SOS1, NCOA1,IL1B,NCOR1,NRIP1,NCOR2,CITED2,SCAND1,PDGFRB
Colorectal Cancer Metastasis Signaling	0.046773514	MMP20,JAK1,GNB5,WNT6,CCND1,PDGFC,TCF7,VEGFA,TGFBR2,MYC,JU N,RHOB,SOS1,PRKAR1B,CTNNB1,NOS2,MMP17,ADCY9,PIK3C2B,SRC,LR P5,ADCY2,AKT2,GNAS,WNT9B,ADCY3,MMP2,IFNGR1,PIK3R3,BCL2L1,WN T8A,MSH6,TGFB3,PIK3CB,FZD5,LEF1,ADCY7,LRP1,TCF7L2,PRKAR1A
Thyronamine and Iodothyronamine Metabolism	0.047863009	DIO3,DIO2
D-glucuronate Degradation I	0.047863009	CRYL1,DCXR
Thyroid Hormone Metabolism I (via Deiodination)	0.047863009	DIO3,DIO2
Tryptophan Degradation X (Mammalian, via Tryptamine)	0.050118723	ALDH1A1,ALDH1A3,ALDH3A2,SMOX,ALDH3A1
Phosphatidylglycerol Biosynthesis II (Non-plastidic)	0.050118723	AGPAT4,GPAM,LCLAT1,MBOAT2,AGPAT3

Supplementary Table 12: All HEPG2 (ENCODE) TCF7L2 Ingenuity Conical pathways with at least nominal $P<0.05$

Ingenuity Canonical Pathways	P-value	B-H Mutipule testing correction p-value	Molecules
Wnt/ β -catenin Signaling	4.2658E-07	0.000128825	FZD10,TGFBR3,TLE1,KREMEN1,FZD1,CCND1,TCF7,SOX2,TGFBR2,MYC,SOX9,JUN,MAP3K7,TGFB2,AKT3,DKK2,PPP2R2C,SOX18,CTNNB1,SOX5,SOX4,SRC,A XIN2,LRP5,GJA1,MDM2,CDH2,WNT8A,SOX6,WNT10A,TLE4,TLE3,TGFB3,DKK4,FZD5,DKK1,PPP2R1B,ACVR2A,LRP1,TCF7L2
Factors Promoting Cardiogenesis in Vertebrates	5.12861E-07	0.000128825	FZD10,NODAL,BMP4,BMP2,TGFBR3,FZD1,TCF7,TGFBR2,MAP3K7,TGFB2,CTN NB1,PRKD1,PRKCA,SMAD2,LRP5,PRKCQ,TDGF1,BMP5,BMPR1B,MAPK14,TGF B3,FZD5,DKK1,TCF7L2,LRP1,ACVR2A
Aryl Hydrocarbon Receptor Signaling	1.86209E-06	0.00030903	ALDH4A1,NFIX,CCND1,NR2F1,MYC,ALDH1A1,JUN,ALDH3A2,TGFB2,GSTA1,AL DH3A1,NFE2L2,AHR,GSTA2,SRC,NFIC,MED1,NQO1,CDK6,SLC35A2,MDM2,NC OA3,RXRg,MGST2,NFIA,TGFB3,IL1B,ALDH1A1,NRIP1,NCOR2,DCT,GSTO2,ES R1
LPS/IL-1 Mediated Inhibition of RXR Function	5.62341E-06	0.000691831	ABCG8,ALDH4A1,ABCG5,LIPC,NR1H4,HS3ST3A1,ABC1,IL1R2,HS6ST1,JUN,A LDH1A1,SCARB1,UST,MAP3K7,ALDH3A2,ACSL5,CYP7A1,FABP1,ACSL4,GSTA1 ,IL1RAP,ALDH3A1,SLC10A1,GSTA2,ACSL3,MGMT,ACSL6,SLC35A2,IL1R1,SULT 1E1,SULT2B1,APOC1,HS3ST3B1,FABP2,MGST2,SREBF1,CAT,IL1B,ALDH1A1, GSTO2,HS3ST5,SULT1B1,ACSL1,MAOA
Ethanol Degradation II	2.45471E-05	0.002454709	ALDH4A1,ACSL3,ACSS3,ALDH1A1,RDH14,DHRS2,ALDH3A2,PECR,ALDH3A1,A CSL1,ADH4,DHRS4
LXR/RXR Activation	4.36516E-05	0.003630781	ABCG8,ABCG5,APOA4,APOB,APOH,NR1H4,APOA2,ARG2,ABC1,IL1R2,LYZ,CY P7A1,SERPIN A1,NOS2,IL1RAP,AGT,AHSG,CD36,IL1R1,APOC1,RXRg,KNG1,AL B,SREBF1,IL1B,NCOR2,FGA,HMGCR
PPAR α /RXR α Activation	7.76247E-05	0.005495409	APOA2,TGFBR3,KRAS,GNA14,GK,ABC1,IL1R2,NR2F1,TGFBR2,JUN,MAP3K7,T GFB2,PRKAA2,PRKAR1B,PLC21,GOT2,IL1RAP,ITGB5,PRKCA,SMAD2,GRB2,ME D1,CD36,IL1R1,NCOA3,MAPK14,IRS1,PRKACG,TGFB3,IL1B,NCOR2,ADIPOR2,A CVR2A,PRKAR1A
FXR/RXR Activation	0.000120226	0.00616595	BAAT,PPARG,ABCG8,ABCG5,SDC1,APOB,LIPC,UGT2B4,CYP27A1,FOXA1,NR1 H4,CYP8B1,FOXO1,SCARB1,ABC4,SREBF1,CYP7A1,AKT3,IL1B,HNF4A,SLC O1B3
Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis	0.000123027	0.00616595	FZD10,BMP4,PTK2B,NFATC3,PIK3R1,BMP2,TAB2,FZD1,TCF7,IL1R2,NFAT5,JUN ,RUNX2,MAP3K7,DKK2,AKT3,CTNNB1,BIRC3,IL1RAP,PPP3CA,ITGB1,SRC,LRP5 ,SPP1,ITGA2,IL1R1,GSN,BMP5,IL17A,BMPR1B,WNT8A,MAPK14,FOXO1,WNT10 A,DKK4,NFATC2,IL1B,FZD5,DKK1,LRP1,TCF7L2
Bile Acid Biosynthesis, Neutral Pathway	0.000134896	0.00616595	BAAT,AKR1C1/AKR1C2,AKR1D1,CYP27A1,CYP7A1,AKR1C4,CYP8B1
TR/RXR Activation	0.000141254	0.00616595	AKR1C1/AKR1C2,SLC2A1,MED1,PIK3R1,UCP1,MDM2,HIF1A,DI02,DI03,NCOA3 ,F10,RXRg,KLF9,SCARB1,SREBF1,CYP7A1,AKT3,NCOR2,TBL1XR1,THR8,FGA
Ethanol Degradation IV	0.000147911	0.00616595	ALDH4A1,ACSL3,ACSS3,ALDH1A1,ALDH3A2,CAT,ALDH3A1,ACSL1
Molecular Mechanisms of Cancer	0.000162181	0.00616595	BMP4,PIK3R1,TAB2,KRAS,CCND1,MYC,TGFBR2,E2F6,RHOB,PLCB1,BIRC3,PR KD1,RND2,SMAD2,PRKCA,CASP3,CDK6,RASGRF2,BCL2L1,BMPR1B,MAX,GAB 1,IRS1,ARHGEF16,PRKACG,TGFB3,FZD5,GNAL,FZD10,BMP2,HIF1A,FZD1,GINA 14,JUN,BBC3,MAP3K7,PRKAR1B,TGFB2,AKT3,ARHGEF3,CTNNB1,PRKCA,SRC ,LRP5,GRB2,GNA12,SMAD7,GNA11,MDM2,BMP5,MAPK14,FOXO1,RASGRF1,IHH ,LRP1,PRKAR1A,PSEN1
TGF- β Signaling	0.000295121	0.010471285	SMAD2,NODAL,BMP4,GRB2,BMP2,SMAD7,KRAS,INHBB,TGIF1,INHBA,TGFBR2 ,BMPR1B,JUN,MAPK14,MAP3K7,RUNX2,TGFB3,TGFB2,HNF4A,ACVR2A
Oxidative Ethanol Degradation III	0.000416869	0.013803843	ALDH4A1,ACSL3,ACSS3,ALDH1A1,ALDH3A2,ALDH3A1,ACSL1
Serotonin Degradation	0.000457088	0.014454398	ALDH4A1,UGT2B4,RDH14,DHRS2,UGT2B10,UGT1A1,ALDH1A1,ALDH3A2,PECR ,ALDH3A1,SULT1B1,MAOA,DHRS4,ADH
Xenobiotic Metabolism Signaling	0.000562341	0.016595869	ALDH4A1,LIPC,PIK3R1,KRAS,HS3ST3A1,ANKRA2,HS6ST1,ALDH1A1,UST,CES1 ,MAP3K7,ALDH3A2,GSTA1,PPP2R2C,NOS2,ALDH3A1,NFE2L2,CITED2,PRKD1 ,AHR,PRKCA,GSTA2,PRKCQ,UGT2B4,MED1,MGMT,NQO1,UGT2B10,SULT1E1,U GT1A1,SULT1B1,HS3ST3B1,MAPK14,MGST2,CAT,IL1B,MAP3K8,ALDH1A1,NC OR2,NRIP1,GSTO2,PPP2R1B,HS3ST5,SULT1B1,MAOA
Axonal Guidance Signaling	0.00060256	0.016595869	BMP4,GLI2,ITSN1,NFATC3,PIK3R1,KRAS,ROCK1,NCK2,SEMA3D,PLCB1,PRKD1 ,ITGA4,ACTR2,PAPP,PRKCA,ADAMTS9,ADAM18,MYL12A,PRKACG,FZD5,EPH A2,GNAL,NRP1,MMP21,FZD10,SLT1,BMP2,SEMA6,EPHA4,FZD1,GINA14,PLXN A2,PDGFC,ABLIM1,ROBO1,NFAT5,ACTR3,GL3,PLXNA1,PRKAR1B,AKT3,PSMD 14,SEMA3B,ROBO2,GNB1L,SEMA3F,PPP3CA,PRKCA,ITGB1,PLXNC1,NRP2,GR B2,GNA12,C9orf33,ITGA2,GNA11,EPHA3,BMP5,SEMA3A,WNT8A,WNT10A,TUBB6 ,NFATC2,SEMA3C,PRKAR1A,SEMA7A
Human Embryonic Stem Cell Pluripotency	0.000645654	0.016982437	FZD10,NODAL,BMP4,BMP2,PIK3R1,FZD1,PDGFC,TCF7,SOX2,TGFBR2,TGFB2 ,AKT3,CTNNB1,PDGFRB,SMAD2,SMAD7,TDG1,BMP5,INHBA,WNT8A,BMPR1B ,FOXO1,WNT10A,TGFB3,S1PR1,FZD5,TCF7L2
RhoGDI Signaling	0.000933254	0.023442288	PIP5K1B,GNA14,CDH11,ROCK2,ACTR3,RHOB,ARHGAP12,ARHGEF3,GNB1L,C DH16,DLC1,ITGA4,PRKCA,RND2,ITGB1,ACTR2,SRC,GINA12,ITGA2,CDH6,GNAI 1,RDX,CDH18,WASF1,ARHGAP5,CDH2,MYL12A,ARHGEF16,ARHGAP35,PIP4K2 A,LESR1,GNAL
Stearate Biosynthesis I (Animals)	0.001174898	0.02630268	ACSL3,DHCR24,CYP2E1,ACSL6,ACSL5,GNPAT,ELOVL2,ACSL4,HNF4A,ACSL1
Noradrenaline and Adrenaline Degradation	0.001174898	0.02630268	ALDH4A1,ALDH1A1,RDH14,DHRS2,ALDH3A2,PECR,ALDH3A1,ADH4,DHRS4,MA OA
Role of Tissue Factor in Cancer	0.001513561	0.032359366	ITGB1,SRC,CTGF,PTK2B,CASP3,PIK3R1,GNA12,RPS6KA3,ITGA6,KRAS,GNA14 ,FRK,FGG,BCL2L1,F10,MAPK14,PLCB1,AKT3,IL1B,FGA,ITGB5,PRKCA
Hepatic Cholestasis	0.00162181	0.032359366	ABCG8,ABCG5,NR1H4,CYP8B1,IL1R2,SLC10A1,PRKCA,PRKCQ,TJP2,CYP27A1,IL1R1,ABC B4,SREBF1,PRKACG,IL1B,ESR1,IRAK2,PRKAR1A
Intrinsic Prothrombin Activation Pathway	0.001659587	0.032359366	KNG1,F10,F8,F5,COL10A1,COL18A1,FGA,FGG,COL3A1
RhoA Signaling	0.001737801	0.033884416	ACTR2,PTK2B,NRP2,SEPT9,RTKN,GNA12,RDX,SEPT4,WASF1,PIP5K1B,PLD1,A RHGAP5,ROCK2,MYLK,MYL12A,ACTR3,PLXNA1,ARHGAP12,ARHGAP35,DLC1 ,SEMA3F,PIP4K2A,CD42EP4

PXR/RXR Activation	0.001819701	0.033884416	GSTA2,ALDH1A1,FOXO1,ALDH3A2,PRKACG,PRKAR1B,CYP7A1,AKT3,GSTA1,I
Coagulation System	0.002511886	0.043651583	KNG1,F10,F8,SERPINA5,F5,SERPINA1,TFPI,FGA,A2M,FGG
VDR/RXR Activation	0.002630268	0.044668359	LRP5,CYP24A1,SPP1,PRKCQ,MED1,NCOA3,RXRG,FOXO1,RUNX2,TGFB2,CEBPA,IGFBP1,SEMA3B,NCOR2,PRKD1,HSD17B2,PRKCA
Caveolar-mediated Endocytosis Signaling	0.002818383	0.046773514	ITGB1,FLNB,COPZ1,SRC,ITSN1,ITGA2,ITGA6,ALB,CD55,ITGA9,PTPN1,ITGB4,ITGA7,ITGB5,PRKCA,ITGA4
Putrescine Degradation III	0.004168694	0.064565423	ALDH4A1,ALDH1A1,ALDH3A2,SAT1,ALDH3A1,MAOA
Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	0.004265795	0.064565423	IL6ST,FZD10,FN1,NFATC3,PIK3R1,KRAS,FZD1,CCND1,PDGFC,TCF7,ROCK2,MYC,IL1R2,NFAT5,JUN,MAP3K7,CEBPA,DKK2,AKT3,PLCB1,CTNNB1,NOS2,IL1RAP,PPP3CA,PRKD1,PRKCA,TRAF1,SRC,SELE,LRP5,PRKCQ,DAAM1,IL1R1,IL17A,WNT8A,MAPK14,WNT10A,DKK4,NFATC2,IL1B,FZD5,DKK1,LRP1,TCF7L2,IRAK2
Arginine Degradation I (Arginase Pathway)	0.004265795	0.064565423	ALDH4A1,OAT,ARG2
Acute Phase Response Signaling	0.004570882	0.064565423	IL6ST,FN1,APOH,PIK3R1,APOA2,SOCS6,KRAS,CP,SERPINA3,NR3C1,FGG,MBL2,JUN,F8,ITIH2,MAP3K7,AKT3,SERPINA1,IL1RAP,AGT,GRB2,AHSG,IL1R1,ALB,MAPK14,IL1B,FGA,A2M,SOCS5
Actin Nucleation by ARP-WASP Complex	0.004570882	0.064565423	NCK2,ROCK2,ITGB1,RND2,ACTR2,ACTR3,RHOB,GRB2,GNA12,ITGA2,WASF1,KRAS,ITGA4
HER-2 Signaling in Breast Cancer	0.004897788	0.067608298	ITGB1,PRKCQ,GRB2,PIK3R1,CDK6,MDM2,KRAS,CCND1,AREG/AREGB,FOXO1,AKT3,ITGB4,PARD3,ITGB5,PRKD1,PRKCA
Histamine Degradation	0.005370318	0.072443596	ALDH4A1,HNMT,ALDH1A1,ALDH3A2,ALDH3A1
Inhibition of Angiogenesis by TSP1	0.005623413	0.074131024	TGFBR2,JUN,MAPK14,SDC1,HSPG2,CASP3,THBS1,CD36,AKT3
Netrin Signaling	0.005888437	0.074131024	NCK2,ENAH,NFAT5,NFATC3,PRKACG,PRKAR1B,NFATC2,ABLIM1,PPP3CA,PRKAR1A
γ -linolenate Biosynthesis II (Animals)	0.005888437	0.074131024	ACSL3,ACSL6,ACSL5,ACSL4,CYB5A,ACSL1
Type II Diabetes Mellitus Signaling	0.006606934	0.081283052	PPARG,ACSL3,PRKCQ,PIK3R1,ACSL6,SOCS6,CD36,MAP3K7,SLC2A2,IRS1,ACSL5,PRKAA2,AKT3,ACSL4,IRS2,ADIPOR2,SOCS5,SMPD3,ACSL1,PRKD1,PRKCA
BMP signaling pathway	0.007079458	0.083176377	BMP4,FST,GRB2,BMP2,SMAD7,KRAS,BMP5,BMPR1B,JUN,MAPK14,MAP3K7,RUNX2,PRKACG,PRKAR1B,PRKAR1A
Neuregulin Signaling	0.007413102	0.085113804	ITGB1,SRC,PRKCQ,GRB2,PIK3R1,ITGA2,KRAS,TMEFF2,AREG/AREGB,MYC,ERBB4,GRB7,AKT3,PRKD1,PSEN1,PRKCA,ITGA4
Fatty Acid Activation	0.007943282	0.087096359	ACSL3,ACSL6,ACSL5,ACSL4,ACSL1
Epithelial Adherens Junction Signaling	0.007943282	0.087096359	MYH10,TGFBR3,PVRL3,MLT4,KRAS,TCF7,CLIP1,TGFBR2,ACTR3,SORBS1,TGFBR2,AKT3,CTNNB1,SRC,ACTR2,LMO7,WASF1,PTPRM,CDH2,TUBB6,MYH9,PARD3,MAGI2,TCF7L2,ACVR2A
Valine Degradation I	0.008128305	0.087096359	HIBCH,BCAT1,ABAT,AUH,ACADS,BCDKDH
Hepatic Fibrosis / Hepatic Stellate Cell Activation	0.008317638	0.087096359	SMAD2,MYH10,CTGF,FN1,IFNGR2,SMAD7,BAMBI,IFNGR1,IL1R1,PDGFC,TGFBR2,IL1R2,EDN1,CYP2E1,TGFBR3,TGFBR2,MYH9,IL1B,A2M,IL1RAP,AGTR1,COL3A1,AGT,PDGFRB
Signaling by Rho Family GTPases	0.008317638	0.087096359	SEPT9,PTK2B,NOX3,PIK3R1,GNA14,PIP5K1B,CLIP1,CDH11,ROCK2,MYLK,JUN,ACTR3,RHOB,ARHGEF3,CDH16,GNB1L,ITGA4,ITGB1,RND2,ACTR2,GNA12,ITGA2,GNA11,CDH6,RDX,SEPT4,CDH18,WASF1,PLD1,CDH2,MYL12A,ARHGEF16,PARD3,PIP4K2A,GNAL,CDC42EP4
Protein Kinase A Signaling	0.009120108	0.09332543	MYH10,NFATC3,PDE3A,TCF7,TGFBR2,ROCK2,MYLK,TH,PHKB,CDKN3,PLCB1,PDE11A,PRKD1,H1F0,PTPRG,PRKCQ,ITPR2,PTPRM,PTP4A1,EPM2A,MYL12A,ITPR3,PRKACG,TGFBR3,AKAP12,FLNB,PTK2B,PPP1R3C,DUSP6,PTPN14,NFAT5,GLI3,DUSP10,PTPN1,PRKAR1B,TGFBR2,CTNNB1,GNB1L,PPP3CA,PRKCA,ATF1,GNA11,AKAP6,PDE4D,ADD3,CDC14B,NFATC2,PDE5A,IHH,CNGB1,TCF7L2,PRKAR1A,DUSP16
Mouse Embryonic Stem Cell Pluripotency	0.009332543	0.09332543	IL6ST,FZD10,ID2,BMP4,GRB2,PIK3R1,KRAS,FZD1,TCF7,MYC,SOX2,ID1,MAPK14,MAP3K7,AKT3,FZD5,CTNNB1,TCF7L2
Heparan Sulfate Biosynthesis (Late Stages)	0.009549926	0.09332543	HS3ST3B1,AADC,HS6ST1,UST,EXT1,EXTL3,SULT1E1,HS3ST5,HS3ST3A1,SUL1T1B1,SULT2B1
Acetate Conversion to Acetyl-CoA	0.009772372	0.09332543	ACSL3,ACSS3,ACSL1
RAR Activation	0.01	0.09332543	TRIM24,BMP2,PIK3R1,NR2F1,ALDH1A1,JUN,PRKAR1B,TGFBR2,AKT3,SORBS3,NT5C1B,PRKD1,CITED2,PRKCA,SMAD2,SRC,PRKCQ,RDH14,MED1,SMAD7,RXRG,MAPK14,PRKACG,TGFBR3,NRIP1,NCOR2,PRKAR1A,ADH4
Colorectal Cancer Metastasis Signaling	0.010964782	0.097723722	IL6ST,FZD10,MM20,PIK3R1,KRAS,FZD1,CCND1,PDGFC,TCF7,TGFBR2,MYC,JUN,RHOB,TGFBR2,PRKAR1B,AKT3,CTNNB1,NOS2,GNB1L,PTGER4,RND2,SMAD2,SRC,LRP5,CASP3,GRB2,IFNGR1,BCL2L1,WNT8A,WNT10A,PRKACG,TGFBR3,FZD5,LRP1,TCF7L2,PRKAR1A
UDP-D-xylene and UDP-D-glucuronate Biosynthesis	0.010964782	0.097723722	UXS1,UGDH
Superpathway of Citrulline Metabolism	0.011220185	0.097723722	OAT,ARG2,ALDH1A1,NOS2,CPS1
Phenylalanine Degradation IV (Mammalian, via Side Chain)	0.011220185	0.097723722	HPD,ALDH3A2,GOT1,GOT2,MAOA
Amyotrophic Lateral Sclerosis Signaling	0.011481536	0.1	GRIN2B,GRIN2A,CACNA1D,CASP3,PIK3R1,PDGFC,BCL2L1,GRID1,GRIK4,CAT,SLC1A2,AKT3,GLUL,CAPN2,CAPN7,BIRC3,RNF19A,PPP3CA
ILK Signaling	0.013803843	0.115877736	MYH10,FLNB,FN1,BMP2,PIK3R1,HIF1A,CCND1,PDGFC,NCK2,MYC,JUN,RHOB,PPAP2B,AKT3,PAPP2R2C,IRS2,ITGB4,CTNNB1,NOS2,ITGB5,DSP,ITGB1,RND2,CASP3,FERMT2,LIMS1,IRS1,MYH9,PPP2R1B
Maturity Onset Diabetes of Young (MODY) Signaling	0.014125375	0.116949939	FABP2,CACNA1D,ALDOB,SLC2A2,FABP1,HNF4A
Glioblastoma Multiforme Signaling	0.016218101	0.132739446	RND2,SRC,FZD10,ITPR2,GRB2,PIK3R1,CDK6,MDM2,KRAS,FZD1,PDGFC,CCND1,MYC,E2F6,WNT8A,FOXO1,WNT10A,RHOB,ITPR3,PLCB1,AKT3,FZD5,CTNNB1,PDGFRB
Cholecystokinin/Gastrin-mediated Signaling	0.017378008	0.138356638	RND2,SRC,PRKCQ,PTK2B,GRB2,ITPR2,GNA12,KRAS,EPHA4,ROCK2,JUN,MAPK14,RHOB,ITPR3,PLCB1,IL1B,PRKD1,PRKCA
Dopamine Degradation	0.018197009	0.142232879	ALDH4A1,ALDH1A1,ALDH3A2,ALDH3A1,SULT1B1,MAOA
Prolactin Signaling	0.018620871	0.143548943	PRKCQ,GRB2,PIK3R1,SOC56,KRAS,NR3C1,TCF7,MYC,JUN,IRS1,PRLR,SOCS5,PRKD1,PRKCA
nNOS Signaling in Neurons	0.019054607	0.146217717	GRIN2B,GRIN2A,PRKCQ,CAPN2,CAPN7,NOS1AP,RASD1,PPP3CA,PRKD1,PRKCA
G Beta Gamma Signaling	0.019952623	0.151008015	SRC,PRKCQ,GRB2,GNA12,GNA11,KCNJ3,KRAS,GNA14,PRKACG,PRKAR1B,AKT3,GNB1L,GNAL,PRKD1,PRKAR1A,PRKCA

Extrinsic Prothrombin Activation Pathway	0.020417379	0.151008015	F10,F5,TFPI,FGA,FGG
Tryptophan Degradation X (Mammalian, via Tryptamine)	0.020417379	0.151008015	ALDH4A1,ALDH1A1,ALDH3A2,ALDH3A1,MAOA
Methylglyoxal Degradation III	0.021877616	0.15703628	AKR1C1/AKR1C2,CYP2E1,AKR1C4,ADH4
Virus Entry via Endocytic Pathways	0.021877616	0.15703628	ITGB1,SRC,FLNB,PRKCQ,ITSN1,PIK3R1,ITGA2,ITGA6,KRAS,CD55,ITGB4,CXADR,ITGB5,PRKD1,PRKCA,ITGA4
Polyamine Regulation in Colon Cancer	0.022908677	0.158489319	PPARG,MYC,MAX,SAT1,KRAS,CTNNB1
IGF-1 Signaling	0.023442288	0.162929603	CTGF,GRB2,PIK3R1,SOCS6,KRAS,NEDD4,NOV,JUN,FOXO1,IRS1,PRKACG,PRKAR1B,AKT3,IRS2,IGFBP1,SOCS5,PRKAR1A
PPAR Signaling	0.024547089	0.165958691	PPARG,GRB2,MED1,KRAS,IL1R1,PDGFC,IL1R2,NR2F1,JUN,MAP3K7,IL1B,NRIP1,NCOR2,IL1RAP,CITED2,PDGFRB
Sertoli Cell-Sertoli Cell Junction Signaling	0.025118864	0.167109061	SPTBN1,TGFB3,PVRL3,MLLT4,KRAS,JUN,SORBS1,MAP3K7,PPAP2B,PRKAR1B,AKT3,MTMR2,CTNNB1,NOS2,ITGA4,ITGB1,SRC,TJP2,ITGA2,MAPK14,TUBB6,PRKACG,TGFB3,MAP3K8,MAGI2,A2M,PRKAR1A
Heparan Sulfate Biosynthesis	0.025703958	0.169824365	HS3ST3B1,AADC,HS6ST1,UST,EXT1,EXTL3,SULT1E1,HS3ST5,HS3ST3A1,SUL1T1B1,SULT2B1
Regulation of Cellular Mechanics by Calpain Protease	0.025703958	0.169824365	ITGB1,SRC,GRB2,ITGA2,CDK6,CNGB1,KRAS,CAPN2,CAPN7,CCND1,ITGA4
Mitochondrial L-carnitine Shuttle Pathway	0.026915348	0.170215851	ACSL3,ACSL6,ACSL5,ACSL4,ACSL1
PI3K/AKT Signaling	0.026915348	0.170215851	ITGB1,GRB2,PIK3R1,ITGA2,GDF15,KRAS,MDM2,CCND1,INPP5D,SYNJ2,BCL2L1,FOXO1,GAB1,LIMK1,AKT3,PP2R2C,MAP3K8,CTNNB1,PPP2R1B,ITGA4
Retinoate Biosynthesis I	0.027542287	0.170215851	ALDH1A1,RDH14,BMP2,NT5C1B,AKR1C4,ADH4,DHRS4
Fatty Acid β -oxidation I	0.027542287	0.170215851	ACSL3,AUH,ACSL6,ACSL5,ACSL4,HSD17B4,ACSL1
Basal Cell Carcinoma Signaling	0.028840315	0.177827941	FZD10,BMP4,GLI2,BMP2,FZD1,BMP5,TCF7,WNT8A,GLI3,WNT10A,FZD5,CTNNB1,TCF7L2
Thyronamine and Iodothyronamine Metabolism	0.030902954	0.177827941	DIO3,DIO2
Ascorbate Recycling (Cytosolic)	0.030902954	0.177827941	GSTO2,GLRX
Thyroid Hormone Metabolism I (via Deiodination)	0.030902954	0.177827941	DIO3,DIO2
Glutamate Degradation II	0.030902954	0.177827941	GOT1,GOT2
Aspartate Biosynthesis	0.030902954	0.177827941	GOT1,GOT2
Germ Cell-Sertoli Cell Junction Signaling	0.031622777	0.179887092	RND2,ITGB1,SRC,PIK3R1,PVRL3,ITGA2,ITGA6,MLLT4,KRAS,GSN,TGFBR2,CDH2,MAPK14,TUBB6,RHOB,MAP3K7,SORBS1,PPAP2B,TGFB3,TGFBR2,MAP3K8,MTMR2,CTNNB1,A2M
IL-12 Signaling and Production in Macrophages	0.032359366	0.18238957	PPARG,APOA4,APOB,PRKCQ,PIK3R1,APOA2,IFNGR1,APOC1,ALB,LYZ,MAPK14,JUN,TGFB3,TGFB2,AKT3,SERPINA1,MAP3K8,REL,NOS2,PRKD1,PRKCA
Cardiomyocyte Differentiation via BMP Receptors	0.033884416	0.188364909	BMPR1B,BMP4,MAP3K7,BMP2,BMP5
Thyroid Hormone Metabolism II (via Conjugation and/or Degradation)	0.033884416	0.188364909	UGT2B4,UGT2B10,UGT1A1,DIO3,DIO2,SULT1B1
Role of NANOG in Mammalian Embryonic Stem Cell Pluripotency	0.034673685	0.190107828	IL6ST,FZD10,BMP4,GRB2,BMP2,PIK3R1,KRAS,FZD1,BMP5,SOX2,WNT8A,BMPR1B,WNT10A,GAB1,GATA6,AKT3,FZD5,CTNNB1
PTEN Signaling	0.038904514	0.208929613	ITGB1,CASP3,GRB2,TGFB3,PIK3R1,ITGA2,KRAS,FOXG1,CCND1,INPP5D,TGFBR2,SYNJ2,BCL2L1,BMPR1B,FOXO1,AKT3,MAGI2,ITGA4,PDGFRB
NF- κ B Activation by Viruses	0.038904514	0.208929613	ITGB1,ACTR2,PTK2B,NOX3,PIK3R1,ITGA2,WASF1,KRAS,PIP5K1B,PLD1,MCF2L,JUN,ACTR3,PARD3,PIP4K2A,NCKAP1,ITGA4
Rac Signaling	0.039810717	0.208929613	ALDH4A1,ALDH1A1,ALDH3A2,ALDH3A1
Fatty Acid α -oxidation	0.039810717	0.208929613	SH3BP4,APOA4,APOB,RAB4A,PIK3R1,APOA2,SH3GLB1,PDGFC,LYZ,FGF10,ACTR2,GRB2,MDM2,FGF6,APOC1,ALB
Clathrin-mediated Endocytosis Signaling	0.040738028	0.212813905	ITGB1,PRKCQ,CD4,PIK3R1,ITGA2,ITGA6,KRAS,AKT3,EIF2AK2,ITGB5,PRKD1,P
Citrulline Biosynthesis	0.043651583	0.221309471	OAT,ARG2,ALDH18A1

Supplementary Table 13: Enrichment of GWAS signals for a randomly generated list of 5,000 genes from the 19,015 RefSeq genes used by HOMER

	Random: 5,000 Genes		
	% tot hg19 gene list	% Chip-Seq gene list	P-values: Chi Square
Endocrine	26.3% (5,000/19,015)	23.7% (210.76/888)	0.20
T2D	26.3% (5,000/19,015)	20.1% (16.5/82)	0.37
Cancer	26.3% (5,000/19,015)	24.3% (81.43/335)	0.50
Cardiovascular	26.3% (5,000/19,015)	23.8% (110.31/463)	0.34
Inflammation	26.3% (5,000/19,015)	23.0% (119.82/521)	0.20
Neuropsychiatric	26.3% (5,000/19,015)	23.2% (135.3/584)	0.18
All	26.3% (5,000/19,015)	21.0% (758.81/3607)	2.07x10 ⁻⁷