Sepsis-associated Pathways Segregate Cancer Groups

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Abstract

Background: Sepsis and cancer are both leading causes of death, and occurrence of any one, increases the likelihood of the other. While cancer patients are susceptible to sepsis, survivors of sepsis are also susceptible to develop certain cancers. This mutual dependence for susceptibility suggests shared biology between the two disease categories. Earlier analysis had revealed cancer-related pathway to be up-regulated in Septic Shock (SS), an advanced stage of sepsis. This has motivated a more comprehensive comparison of the transcriptomes of SS and cancer.

Methods: Gene Set Enrichment Analysis was performed to detect the pathways enriched in SS and cancer. Thereafter, hierarchical clustering was applied to identify relative segregation of 17 cancer types in to two groups *vis-a-vis* SS. Biological significance of the selected pathways was explored by network analysis. Clinical significance of the pathways was tested by survival analysis. A robust classifier of cancer groups was developed based on machine learning.

Results: A total of 66 pathways were observed to be enriched in both SS and cancer. However, clustering segregated cancer types into two categories based on the direction of transcriptomic change. In general, there was up-regulation in SS and one group of cancer (termed Sepsis-Like Cancers, or SLC), but not in other cancers. SLC group mainly consisted of malignancies of the gastrointestinal tract (head and neck, oesophagus, stomach, liver and biliary system) often associated with infection. Machine learning classifier successfully segregated the two cancer groups with high accuracy (> 98%). Additionally, pathway up-regulation was observed to be associated with survival in the SLC group of cancers.

Conclusion: Transcriptome-based systems biology approach segregates cancer into two groups (SLC and CA) based on similarity with SS. Host response to infection plays a key role in pathogenesis of SS and SLC. However, we hypothesize that some component of the host response is protective in both SS and SLC.

Keywords: Sepsis, Septic shock, Cancer, KEGG Pathway, TCGA, GEO

Background

Sepsis is a potentially life-threatening complication caused by dysregulated host response to infection, often leading to organ failure and death. Estimated global burden of sepsis is more than 48.9 million people in 2017 with 11 million deaths [1]. Septic shock is the advanced stage of sepsis with metabolic dysregulation and uncontrolled hypotension. Several epidemiological studies have linked sepsis and cancer [2, 3]. Liu *et al.* [2] conducted an association study between sepsis and ensuing risk of cancer in elderly adult population of the United States, and observed that sepsis is significantly associated with increased risk for many cancers including chronic myeloid leukemia, myelodysplastic syndrome, acute myeloid leukemia, cancers of the cervix, liver, lung, rectum, colon. Another association study revealed 2.5 fold increased risk of sepsis in survivors of cancer in

community-dwelling adults (the risk is increased up to 10 times in hospitalized cancer patients) [3]. Co-occurrence of cancer with sepsis is associated with higher mortality than sepsis alone without cancer [4]. On the other hand, sepsis is a common cause of death in critically ill patients with cancer, with high ICU and hospital mortality [5–7]. Interestingly, mortality due to sepsis varies widely from 42 to 82% across cancer tissue types [8], suggesting varying likelihood of survival of patients suffering from different cancers.

This study is motivated by multiple shared features of septic shock (SS) and cancer. There is co-occurrence of the two entities, with synergistic effect on mortality. Both are associated with inflammation at some stage of the disease. Inflammation is well understood to promote malignant growth with participation of diverse immune cells and molecules, such as, cytokines [9]. Similarly, sepsis is understood as a non-resolving inflammatory response to infection that leads to organ dysfunction [10]. Both the diseases are associated with anaerobic metabolism with lactic acidosis being a hallmark of septic shock [9, 11]. In our earlier work, we have observed a cancer associated pathway to be significantly up-regulated in septic shock [12]. Additionally, there are previous reports on shared molecular changes in sepsis and cancer. Bergenfelz *et al.* [13] reported that Wnt5a induces immunosuppressive phenotype of macrophages in sepsis and breast cancer patients. HMGB1, a key late inflammatory mediator of systemic inflammatory response syndrome associated with bacterial sepsis, is also implicated in tumorigenesis and disease progression [14]. Muscle wasting - observed in patients with cancer, severe injury and sepsis - is associated with increased expression of several genes, particularly transcription factors and nuclear cofactors, regulating different proteolytic pathways [15]. Methodologically, all of these studies employed gene-level analysis, i.e., considering gene as the functional unit. On the other hand, a gene set or pathway represents coordinated molecular activity and represents a higher-order functional unit in a tissue or cell. Pathway-level analysis allows detection of a cumulative signal that is not accessible at the gene-level. To our knowledge, there is no report in literature on pathway-level comparison between sepsis and cancer. In the present study, we have performed unbiased analysis of SS and cancer datasets to discover shared patterns of pathway-level transcriptional alteration underlying the two illnesses.

Methods

Gene expression data
TCGA data: Gene expression data as FPKM (Fragments Per Kilobase of transcript per Million mapped reads) values were retrieved from The Cancer Genome Atlas (TCGA) database (https://portal.gdc.cancer.gov/) on July 5, 2018 for 17 different human cancers i.e., bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), cholangiocarcinoma (CHOL), colon adenocarcinoma (COAD), esophageal carcinoma (ESCA), head and neck squamous cell carcinoma (HNSC), kidney chromophobe (KICH), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), prostate adenocarcinoma (PRAD), rectum adenocarcinoma (READ), stomach adenocarcinoma (STAD), thyroid carcinoma (THCA) and uterine corpus endometrial carcinoma (UCEC). For each cancer type, TCGA project code was provided in the search field and RNA-seq data for paired samples (each pair consisting of tissue from tumour zone and tissue from adjacent unaffected zone in the same individual) were downloaded. In all, gene expression data were derived from 687 patients with cancer. Data were transformed to logarithmic scale (base 2).
GEO data: Six studies of septic shock (SS) were selected following the procedure described earlier [12]. Normalized gene expression data from the series matrix files were retrieved from NCBI Gene

Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/) on April 10, 2019. Data were transformed to logarithmic scale (base 2). Expression intensity for each Entrez gene ID was calculated after removing duplicated probe sets. Genes common to all SS studies were included in the analysis. In all, gene expression data were derived from 445 patients with SS and 116 control subjects. Redundant samples (other than control and SS) were excluded from analysis.

Characteristics of 23 distinct data sets used in the current study (6 of SS and 17 of cancer) are listed in Table 1. Each data set consisted of transcriptome-wide expression data from a number of patients suffering from a single disease (SS or cancer). For SS, each data set consisted of blood transcriptome data. For cancer, each data set consisted of transcriptome data from a tissue. Control was defined as adjacent normal tissue for cancer (TCGA), and a healthy subject for SS (GEO).

Table 1: Characteristics (such as tissue of origin, source database, disease type, sample size of each study and details about the platform technology used to generate the data) of the 23 data sets (17 cancer + 6 septic shock) included in the analysis. Study_code refers to the code assigned by the source database (either TCGA or GEO) to the data set. TCGA stands for The Cancer Genome Atlas. GEO stands for NCBI Gene Expression Omnibus. Paired control refers to adjacent normal tissue in the same cancer patient. Technology for transcriptome assay is either sequencing (RNA-seq) or hybridization-based microarray (Affymetrix).

Study_Code	Data source	Disease	Tissue	Number of samples	Paired control	Technology
BLCA	TCGA	Cancer	Bladder	38	Yes	RNA-seq (Illumina)
BRCA	TCGA	Cancer	Breast	220	Yes	RNA-seq (Illumina)
CHOL	TCGA	Cancer	Gallbladder, liver and parts of biliary tract	18	Yes	RNA-seq (Illumina)
COAD	TCGA	Cancer	Colon and rectosigmoid junction	82	Yes	RNA-seq (Illumina)
ESCA	TCGA	Cancer	Esophagus	16	Yes	RNA-seq (Illumina)
HNSC	TCGA	Cancer	Base of tongue, floor of mouth, gum, hypo- and oro-pharynx, larynx, etc.	86	Yes	RNA-seq (Illumina)
KICH	TCGA	Cancer	Kidney	48	Yes	RNA-seq (Illumina)
KIRC	TCGA	Cancer	Kidney	144	Yes	RNA-seq (Illumina)
KIRP	TCGA	Cancer	Kidney	64	Yes	RNA-seq (Illumina)
LIHC	TCGA	Cancer	Liver and intrahepatic bile ducts	100	Yes	RNA-seq (Illumina)
LUAD	TCGA	Cancer	Bronchus and lung	114	Yes	RNA-seq (Illumina)
LUSC	TCGA	Cancer	Bronchus and lung	98	Yes	RNA-seq (Illumina)
PRAD	TCGA	Cancer	Prostate gland	104	Yes	RNA-seq (Illumina)
READ	TCGA	Cancer	Rectum rectosigmoid junction	20	Yes	RNA-seq (Illumina)

STAD	TCGA	Cancer	Stomach	62	Yes	RNA-seq (Illumina)
THCA	TCGA	Cancer	Thyroid gland	116	Yes	RNA-seq (Illumina)
UCEC	TCGA	Cancer	Corpus uteri	46	Yes	RNA-seq (Illumina)
GSE4607	GEO	Septic Shock	Whole Blood	84	No	Microarray (Affymetrix HGU 133 Plus 2.0)
GSE8121	GEO	Septic Shock	Whole Blood	75	No	Microarray (Affymetrix HGU 133 Plus 2.0)
GSE9692	GEO	Septic Shock	Whole Blood	45	No	Microarray (Affymetrix HGU 133 Plus 2.0)
GSE13904	GEO	Septic Shock	Whole Blood	124	No	Microarray (Affymetrix HGU 133 Plus 2.0)
GSE26378	GEO	Septic Shock	Whole Blood	103	No	Microarray (Affymetrix HGU 133 Plus 2.0)
GSE26440	GEO	Septic Shock	Whole Blood	130	No	Microarray (Affymetrix HGU 133 Plus 2.0)

Pathway Enrichment Analysis

Pathway (gene set) enrichment analysis was performed using the algorithm previously described [12, 16]. Gene sets were defined based on pathways annotated at KEGG [17]. Any pathway with small number (10 or less) of genes was discarded from analysis. For each gene, t-statistic was computed to denote change in gene expression in case group compared to the control group. For each pathway, a score was calculated by weighted averaging (i.e., sum of the gene-level t-statistics divided by the square root of the number of genes in the pathway) of all gene-level t-statistic for the pathway. Significance of the observed pathway score was calculated by permutation testing performed in the following manner. In each permutation, the samples were randomly re-labelled as case and control, with calculation of a simulated pathway score. This was done 10000 times generating 10000 simulated values representing the null distribution of the pathway score. Deviation of the observed pathway score from the null distribution was quantified by the fraction of times that the simulated score was more extreme than the observed score. This result was assigned as permutation p-value of the observed pathway score. Pathway enrichment analysis was performed using code modified from the R function *gseattperm()* of the package **Category** [18].

Cluster Analysis

Pathway scores of all 23 studies (6 SS + 17 cancer) were subjected to hierarchical clustering in the following manner. First, the Euclidean distance matrix was computed to capture the pair-wise dissimilarity among the studies. Thereafter, the distance matrix was subjected to agglomerative hierarchical cluster analysis, with "complete" linkage method. Distance matrix computation and cluster analysis were performed using the R functions *dist()* and *hclust()* respectively. Output of the cluster analysis was plotted as a dendrogram.

Visualization of Pathway-level and Gene-level Expression Scores

A pathway was selected if it was significantly enriched (permutation p < 0.01) in 80% or more of the studies in one or both of the cancer groups (SLC, CA). Pathway score matrix was generated for all selected pathways across all 23 data sets. Heat map was generated with the R function *heatmap.2()* of the package **gplots** [19]. For each pathway, mean pathway score across the disease group was calculated separately. Boxplot of the pathway scores for the three disease groups

(SS, SLC and CA) was drawn using R function *boxplot()*.

For generating gene-level heat map of individual pathway, the following steps were followed. First, average log-expression level was calculated for case group and control group separately. Log2(fold -change) or LFC was calculated by subtracting the average control value from the average case value. This was done for each gene. For each disease type (SS, SLC or CA), median LFC was calculated across the studies in that disease group. Combined heat map was generated based on the pathway genes and the three disease groups. Only those genes with similar LFC directionality in SLC and SS were included in visualization.

Network analysis

Firstly, a background network was constructed by including all the pathways (KEGG) [17] with overlapping gene memberships, i.e., for a pathway to be included, it must share at least 5% of the total number of genes with another pathway. Pathways connected to less than 3 other pathways each were dropped from network analysis. In this network, each pathway was considered a node, and the edge between two nodes represented overlap between the two pathways. In this way, a network was constructed with 244 nodes and 5304 edges. Degree distribution of the network was calculated using the function *degree_distribution()* of the package **igraph** [20]. Plot of the degree distribution of the network was drawn. For each node in the network, degree and betweenness centrality were calculated with the R functions *degree()* and *betweenness()* respectively. In the network diagram, selected pathways were shown as nodes coloured in red. Box plot was drawn to show the difference of degrees between selected set and other pathways.

Sample-level pathway score

Individual pathway scores for the cancer patients were computed in the following manner. For each subject, two genome-wide expression vectors were retrieved from TCGA: one for the tumour tissue (T) and another for the adjacent normal tissue (N). Normalized gene expression vector (E) was then calculated by subtracting the normal expression values from the tumour expression values (E = T - N). For each of the selected 66 pathways, a score (Z) was calculated as the weighted average of the expression of the genes in the pathway (i.e., sum of the individual gene expression scores divided by the square root of the number of genes in the pathway). This resulted in 66 pathway scores for each patient. These individual pathway scores were used for survival analysis.

Machine learning

For the machine learning-based prediction, we retrieved additional transcriptome data for SLC and CA cancers from NCBI GEO. Six datasets containing 542 cancer subjects (of both SLC and CA) and 180 healthy control subjects were included (Additional File 7: Table S4.). The additional validation data sets were required because the TCGA data sets were used for feature selection (i.e., 66 pathways) and segregation of cancer groups (SLC and CA). For each cancer sample, pathway scores were generated by weighted averaging of the gene-level t-statistic between the case group and control group, (i.e., sum of the individual t-statistic divided by the square root of the number of genes in the pathway). The scores of the sixty-six pathways were used as input and the cancer group label (SLC or CA) as output in machine learning-based classification of cancer patients. Support vector machine (SVM) and neural net (NN) classifiers were implemented using R package **MLInterfaces** [21]. SVM was used through function call *Mlearn()* with learning function svmI. Neural Network was used through function call *MLearn()* with learning function nnetI and three nodes in the hidden layer, with weight decay set to 0.01. Confusion matrix from the classifier output of five-fold cross-validation was collected for calculation of misclassification rate (fraction of samples wrongly predicted by the algorithm) and accuracy.

Survival Analysis

Based on the number of cases and available survival information, three SLC cancer types (HNSC, KIRC and LIHC) were selected for survival analysis. The following clinical metadata were collected as provided by TCGA: days (to death or last follow-up) and outcome (survivor or non-survivor). Patient-level (sample-level) pathway score was used for analysis. For each cancer type, the patients were divided into two groups (high-score and low-score) by applying the median pathway score as threshold. Survival plots were generated using the functions in the R package **survival** [22] as described here. First, a survival object was created applying the function *Surv()*, with day and outcome. The output, i.e., the fitted model, was passed to the function *survfit()* that created two survival curves, based on the level of pathway score (high or low). Survival plots were displayed using the function *ggsurvplot()* from the package **survminer** [23]. Significance of the difference between the survival plots of the two curves was calculated by the function *surv_pvalue()* from the same package.

Code and data availability

All programming was done in the R programming language [24]. Data and R code are available at the following link: https://figshare.com/
(https://doi.org/10.6084/m9.figshare.8118413.v3, https://doi.org/10.6084/m9.figshare.8118647.v5). The whole data can be downloaded as a single zip file (tcnibmgdoc.zip). Upon uncompressing the zip, instructions for running the code and generating the figures of this manuscript are available in the file howto.pdf.

Selection of the transcriptome data sets and analysis workflow leading to the final list of 66 significant pathways are described in Fig. 1. The study characteristics of the data sets are listed in Table 1.

Fig. 1: Selection of data and analysis workflow. Left-most column shows the source of data from GEO for SS and TCGA for cancer. Data for SS were applied first followed by data from TCGA. Next column describes the processing of the data that form a progressive filter for narrowing down the number of pathways of relevance. KEGG contains 272 pathways of which 90 were assigned significant pathway score by Gene Set Enrichment Analysis (details in the main text). The right-most column lists the interpretations

made at each horizontal step.

Results

The transcriptomic data for 23 studies (17 cancer and 6 SS) consisted of 687 patients with cancer and 445 with SS. The data were subjected to progressive analysis and pathway filtering (Fig. 1).

Hierarchical clustering revealed two groups of cancers

At the outset, independent of our data, there were a total of 272 pathways in the KEGG database. Application of permutation-based testing of each pathway, revealed that 90 of these were significantly ($p < 0.01$) enriched in each of the 6 SS data sets, thus constituting a robust set of SS-specific pathways. Hierarchical clustering on combined cancer and sepsis data sets for these 90 pathways revealed two groups of cancers, with one group segregating with SS (Additional File 1: Figure S1). The 6 cancers (HNSC, ESCA, STAD, LIHC, CHOL, KIRC) belonging to the SS clade were termed Sepsis-Like Cancer (SLC). The other 11 cancers (BLCA, BRCA, COAD, KICH, KIRP, LUAD, LUSC, PRAD, READ, THCA and UCEC) formed the other clade and were termed the CA (Cancer Alone) group.

In order to exclude those pathways that may be irrelevant to cancer biology, the 90 pathways were tested for enrichment in any or both of the cancer groups (i.e., significantly enriched in at least 80% of a group of cancer). 24 out of the 90 SS-specific pathways were observed not to be associated with any of the two cancer groups. Exclusion of these 24 non-significant pathways resulted in retention of 66 pathways significantly associated with both SS and cancer. Pathway score matrix of these 66 pathways across all diseases (including SS, SLC, CA) was visualized as a heat map (Fig. 2A). The sample dendrogram of this heat map recapitulated the segregation of the cancer groups as observed earlier with 90 pathways (Additional File 1: Figure S1). In general, the heat map demonstrated up-regulation of the pathways in SS and SLC. Further, for each pathway, mean score was calculated across all data sets in one disease group (SS, SLC or CA). Box plot of these scores clearly demonstrated the shared directionality in pathway dysregulation in SS and SLC, i.e., in both these conditions there was up-regulation of the pathway (Fig. 2B). Additionally, the average number of pathways up-regulated in a disease group was observed to be 63, 58 and 11 for SS, SLC and CA respectively (Additional File 4: Table S1), thus establishing general agreement in the direction of pathway transcriptional change between SS and SLC. The overall trend in pathway dysregulation was also reflected in the gene-level heat map for individual pathways (Additional File 2: Figure S2).

Fig. 2: (A) Pathway heat map for 66 selected KEGG pathways where each pathway is significantly perturbed in at least 80% of the studies in one or both of the two groups of cancers. Colour of the cell is explained by the colour key histogram provided on the top left. Green indicated down-regulation of pathway, red indicates up-regulation. In the column-sidebar, purple indicates SS group, cyan indicates SLC group and blue indicates CA group. Positive pathway score is presented in red, negative pathway score in green. (B) Box plot shows group-mean pathway scores for the three groups of diseases. In general, there is pathway up-regulation in SLC group, even higher than that in SS, while down-regulation in CA group.

Network analysis

Genome-level biological significance of the selected pathways was revealed by network analysis. Here, the network consisted of all KEGG pathways as nodes and substantial pairwise gene-overlap among pathways as edges. The centrality of the selected pathways was further quantified in terms of degree and betweenness centrality. Degree captures short-range connectivity of a node (i.e., how many nodes are connected to this node?), while betweenness centrality captures long-range centrality (i.e., how often this node falls on the shortest path between any two other nodes?) Degree captures the number of immediate neighbours of a node, while betweenness captures the essentiality of a node to the structure of the network. The degree and betweenness values for the selected 66 pathways were recorded (Additional File 5: Table S2).

The degree distribution of the network showed scale-free property of a biological network, i.e., many nodes with few edges and a few nodes with large number of edges (Additional File 3: Figure S3 - panel A). Visual exploration revealed the selected pathways at the core of the network (Fig. 3), and this was confirmed by comparing the degree of these 66 pathways with other pathways in the human genome. As shown in Additional File 3: Figure S3 (panel B), selected pathways had higher degree than the other pathways.

Fig. 3: KEGG overlap network is constructed with each KEGG pathway as a node and overlapping gene membership between two pathways as an edge. The selected 66 pathways are shown in red, while the other pathways are shown in grey. Red nodes (selected pathways) have more connecting edges than the grey nodes, thus representing hub-like nature of selected pathways. This suggests that key biological processes are perturbed in both SS and SLC.

Machine learning-based prediction of cancer group (SLC/CA) from 66 pathway scores

In order to assess the clinical relevance of the selected pathways, we asked if it is possible to predict (by a machine learning algorithm) the cancer group based on the selected pathway scores of an individual patient of cancer. For each patient, 66 pathway scores were input for the classifier, with the expected output being SLC or CA. Five-fold cross-validation was employed with balanced partitioning in each fold. Both algorithms - Support Vector Machine (SVM) and Neural Net (NN) – performed with high accuracy in assigning the samples to their respective cancer groups. SVM correctly assigned 537 (99.08%) out of 542 patients , while NN correctly assigned 536 (98.89%) out of 542 patients, with a misclassification rate of 0.9% and 1.1% respectively (Table 2). This independent validation showed the clinical relevance of the selected 66 pathways for prediction of cancer group from individual patient-level data.

Table 2: Two machine learning algorithms - Support Vector Machine (SVM) and Neural Network (NN) - were implemented through the function call MLearn (of R package MLInterfaces). SVM was applied with default parameters. Neural Network applied with three nodes in the hidden layer, with weight decay set to 0.01. Five-fold cross-validation was performed by generating a partition function (for cross-validation, where the partitions are approximately balanced with respect to the distribution of cancer tissue types (SLC or CA) in training and test sets in each fold. Confusion matrix from the classifier output was collected for calculation of misclassification rates.

Support Vector Machine		Predicted	
		CA	SLC
Given	CA	349	1
	SLC	4	188
Misclassification rate			0.9
Neural Network		Predicted	
		CA	SLC
Given	CA	347	3
	SLC	3	189
Misclassification rate			1.1

Survival analysis

Another measure of clinical relevance of pathway signature was provided by its association with survival. For a given pathway, the patients were divided into two groups of subjects (high-scoring and low-scoring) based on the level of pathway score. Survival probability for these two groups was assessed both graphically and statistically. For many of the pathways, there was a higher pathway score in survivors compared to non-survivors in SLC. This directionality was also maintained in SS, i.e., higher pathway score in survivors compared to non-survivors (Additional File 6: Table S3). The number of pathways associated ($p < 0.1$) with survival varied: 9 (14%) in HNSC, 28 (42%) in LIHC and 34 (52%) in KIRC (Fig. 4A). Representative plots were drawn to show survival difference between high-score and low-score patients for the pathway "Fc gamma R-mediated phagocytosis" (Fig. 4B-D).

Fig. 4: (A) Three SLC studies were selected for survival analysis. For each cancer, association with survival was accepted at threshold of p < 0.1. For each cancer type, proportion of pathways associated with survival was calculated and converted to a percentage. The percentage values are presented in this bar plot. As shown, up to 50% of the pathways are associated with survival in the SLC group. (B-D) Kaplan-Meier plot showing significant association between pathway score and survival from the three SLC cancer types: HNSC (B), KIRC (C) and LIHC (D).

Functional classification of the pathways
The selected 66 pathways were divided into categories based on their functional relevance. The categories included: immune system, infection, cancer, catabolism, signal transduction, ribosome biogenesis and carbohydrate metabolism (Additional File 8: Text S1).

Viral integration in TCGA samples
Out of the 687 cancer samples from TCGA analysed by us, there was overlap of 425 (61.9%) samples with the samples analysed for viral integration by Tang *et al.* [25]; of the 425 samples, 120 belonged to SLC group, and 305 belonged to CA group. Viral integration was observed in 9 (7.5%) SLC samples and 2 (0.66%) CA samples, showing significantly (p = 0.0003) higher viral integration in SLC. In another study by Cao *et al.* [26], there was an overlap of 533 (77.6%) of 687 samples analysed by us. Of the 533, 200 (37.5%) were SLC while 333 (62.5%) were CA cancers. There was significantly (p = 0.001) higher viral integration in SLC (30%) compared to CA (17.4%). The report by Kazemian *et al.* [27] was not associated with supplementary sample-level data. However, re-analysis of summary data provided (Additional File 8: Table S5) led to the finding of significantly (p = 4.10E-13) higher viral integration in SLC (18.7%) compared to CA (5.6%). Over all, the findings were consistent with SLC cancers to have greater likelihood of prediction of viral integration.

Discussion

Comprehensive system-level analysis reveals shared transcriptomic response between septic shock (SS) and a subset of cancers (SLC). The SLC group predominantly consists of cancer of the upper GI tract, including head and neck, oesophagus, stomach, liver and biliary tract. The striking segregation of the SLC group with SS suggests shared elements of pathophysiology operational in these disorders. Sixty-six pathways differentially expressed in both SS and SLC represent critical biological processes, such as metabolism, immune response and protection against infection. Network analysis reveals the selected pathways as a core functional module (Figure 3) of the genome-scale network dysregulated in both SS and SLC. Many of these processes, such as metabolism and inflammatory response are known to contribute to the pathogenesis of both sepsis and cancer [9].

The segregation of cancer into two groups (SLC and CA) prompted us to investigate the prospect of the selected pathways as a classifier. Machine learning-based validation of an independent data set proved that the pathways indeed consist of a robust sample-level signature of the cancer groups. It is thus possible to predict, with high accuracy, whether a patient belongs to a particular cancer group (SLC or not). With plummeting costs and increasing acceptability of clinical transcriptomics, this signature may be useful in future for patient stratification.

Similarity in the direction of change in pathway activity immediately evokes an explanation in terms of shared immunological response in either case. SLC are often associated with infection (i.e., human papilloma virus in "head and neck", *H. pylori* in stomach, hepatitis viruses in liver). In fact, TCGA data analysed for the presence of viral sequence reads in RNA-seq datasets of several cancers have revealed infection status of the samples. Interestingly, the majority of the infected samples belong to the GI associated cancers including head and neck (HNSC), oesophagus (ESCA), stomach (STAD) and liver (LIHC) [25–29]. Cao et al. (2016) [26] estimated high percentage of infected samples in TCGA datasets for liver (21.2%), head and neck (16.6%), stomach (14.8%) and oesophagus (12%). It is known that sepsis starts out as an infection, but it is the uncontrolled host response that drives the phase of shock. Similarly, in cancers with an infectious origin, host response (e.g., inflammation) plays a role in malignant transformation [9]. Pathways related to immune response are consistently differentially expressed in both SS and SLC. Although the time scale of pathogenesis is much shorter in SS compared to cancer, our finding calls for greater attention into the shared cellular processes underlying these two distinct clinical phenotypes.

The finding of pathway up-regulation associated with survival brings new insight into the relationship between the shared transcriptomic patterns and disease outcome. Sepsis is a highly lethal dysregulated host response to infection, and SLC, by extension, appears to share a part of that response. Since the pathways are selected on the basis of up-regulation in both SLC and SS (compared to control), plausible explanation is that the pathway up-regulation is protective rather than detrimental to the human host. It is worth mentioning that viral integration or bacterial infection in a setting of cancer has been reported to favour survival in SLC cancers of oropharyngeal [30], liver [31] and kidney [32].

Alteration of intestinal permeability is known in both sepsis and cancer [33]. It may be speculated that anatomical proximity increases the likelihood of the liver and upper gastrointestinal tissue to be exposed to the translocated microbial products through a permeable gut, eliciting a host response in both SS and SLC. Significant association between survival and up-regulation of phagocytosis-associated pathway (i.e., Fc gamma R-mediated phagocytosis) lends support to this view. In general, sepsis is less lethal in patients with cancer of the digestive system than cancer of other organs [8]. The role of gut in survival from sepsis and cancer is an active area of research with translational potential.

Conclusions

Firstly, transcriptome-based systems biology approach segregates cancer into two groups (SLC and CA) based on similarity with SS. Secondly, the similarity is based on a set of pathways associated with pathogenesis of sepsis and cancer. These pathways form a robust signature of a novel cancer grouping. Lastly, up-regulation of the pathways is protective rather than detrimental to the patient. A mechanism of the shared protective host response is hypothesized in terms of immunocompetence induced by microbial products from the permeable gut. This work is the first step towards a systems biology-based patient stratification. It is hoped that future work in this direction shall generate actionable knowledge for clinical management of both cancer and septic shock.

List of abbreviations:

BLCA: Bladder Urothelial Carcinoma
BRCA: Breast invasive carcinoma
CA: Cancer Alone
CHOL: Cholangiocarcinoma
COAD: Colon adenocarcinoma
ESCA: Esophageal carcinoma
FPKM: Fragments Per Kilobase of transcript per Million mapped reads
GEO: Gene Expression Omnibus
HNSC: Head and Neck squamous cell carcinoma
ICU: Intensive Care Unit
KEGG: Kyoto Encyclopaedia of Genes and Genomes
KICH: Kidney Chromophobe
KIRC: Kidney renal clear cell carcinoma
KIRP: Kidney renal papillary cell carcinoma
LFC: log2(fold change)
LIHC: Liver hepatocellular carcinoma
LUAD: Lung adenocarcinoma
LUSC: Lung squamous cell carcinoma
NCBI: National Center for Biotechnology Information
NN: Neural Net
PRAD: Prostate adenocarcinoma
READ: Rectum adenocarcinoma
SLC: Sepsis-Like Cancers
SS: Septic shock
STAD: Stomach adenocarcinoma
SVM: Support Vector Machine
TCGA: The Cancer Genome Atlas
THCA: Thyroid carcinoma
UCEC: Uterine Corpus Endometrial Carcinoma

Declarations

– **Ethics approval and consent to participate**
In this study, patient data from public databases (GEO and TCGA) have been analysed. We have not used any patient data that are not already available in the public domain.

- **Consent to publish**

  Not applicable.
- **Availability of data and materials**

- **Competing interests**

  The authors declare that they have no competing interests.
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- **Authors' contributions**

  SKM conceptualized the study and contributed to Funding Acquisition, Project Administration, Resources, Supervision. HT contributed to Data Curation. SM contributed to Data Curation, Software, Validation, Visualization. All authors contributed to Formal Analysis, Investigation, Methodology, Manuscript writing and approved of the final manuscript.
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- **Authors' information**

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Supplementary Information

Supplementary Figure S1. For the 90 pathways significantly associated with SS, pathway scores were computed for the cancer studies. Scores for SS (6 studies) and cancer (17 studies) were subjected to hierarchical clustering (details in main text). As shown in this dendrogram, there is clear segregation of the cancer studies into two groups: sepsis−like (SLC) and other cancer (CA).

Supplementary Figure S1
For the 90 pathways significantly associated with SS, pathway scores
were computed for the cancer studies. Scores for SS (6 studies) and cancer
(17 studies) were subjected to hierarchical clustering (details in main text).
As shown in this dendrogram, there is clear segregation of the cancer studies
into two groups: sepsis−like (SLC) and other cancer (CA).

Supplementary Figure S2. Gene level heat map of each of the selected 66 pathways. LFC for each gene was calculated from disease and normal samples (disease-normal) for all studies. For each disease type (CA, SLC or SS), median LFC was calculated across the studies in that disease type. Combined heat map was generated based on the pathway genes and the three disease groups. We considered only those genes which have similar LFC directionality in SLC and SS. Red colour represents up-regulation in disease compared to control, while green colour represents down-regulation. Pathway names with KEGG identifiers are shown on the top, gene symbol and names are row-labels of heat map. The major class (to which the pathway belongs) is shown at the bottom.

Supplementary Figure S3. (A) This is the degree distribution of the network generated by overlapping KEGG pathways. This shows that there are many nodes with very low connectivity but a few nodes with very high connectivity. This is consistent with the scale-free property of biological networks. (B) Box plot showing comparison of degree between two groups of nodes in this network - selected 66 and others. The higher value of the selected 66 nodes suggests that these are highly overlapping pathways forming a functional core of the human genome.

Supplementary Table S1 . Selected 66 pathways with their significance and direction of regulation in all the studies. Coloured cells are a representation of pathway scores. Red indicates significant up-regulation, green indicates significant down-regulation and grey indicates non-significant change in pathway. Number of up- and down-regulated pathways in each study is shown at the top. Group membership (to CA, SLC or SS) is shown as a label on top of the code of the data set. First three columns of the sheet are pathway name, annotation (functional class) and KEGG ID respectively.

| | | | Average number of up-regulated pathways: 11 | SLC: 58 | SS: 63 |

| | | | # Up-regulated | 30 | 10 | 5 | 1 | 13 | 19 | 19 | 3 | 4 | 9 | 13 | 63 | 63 | 57 | 42 | 62 | 60 | 63 | 63 | 63 | 63 | 63 |
| # Down-regulated | 0 | 39 | 34 | 65 | 20 | 14 | 32 | 9 | 6 | 12 | 32 | 1 | 1 | 0 | 8 | 1 | 0 | 3 | 3 | 3 | 3 | 3 |

Group labels: CA | SLC | SS

Column codes:
BLCA, BRCA, COAD, KICH, KIRP, LUAD, LUSC, PRAD, READ, THCA, UCEC (CA); LIHC, CHOL, HNSC, KIRC, ESCA, STAD (SLC); GSE13904, GSE26378, GSE26440, GSE4607, GSE8121 (SS)

Pathway name	Annotation	Pathway_id
Pathways in cancer	Cancer	hsa05200
Transcriptional misregulation in cancer	Cancer	hsa05202
Proteoglycans in cancer	Cancer	hsa05205
Renal cell carcinoma	Cancer	hsa05211
Pancreatic cancer	Cancer	hsa05212
Glioma	Cancer	hsa05214
Prostate cancer	Cancer	hsa05215
Melanoma	Cancer	hsa05218
Bladder cancer	Cancer	hsa05219
Acute myeloid leukemia	Cancer	hsa05221
Non-small cell lung cancer	Cancer	hsa05223
Central carbon metabolism in cancer	Cancer	hsa05230
Choline metabolism in cancer	Cancer	hsa05231
Chemical carcinogenesis	Cancer	hsa05204
Galactose metabolism - Homo sapiens (human)	Carbohydrate metabolism	hsa00052
Glycolysis / Gluconeogenesis	Carbohydrate metabolism	hsa00010
Pentose phosphate pathway	Carbohydrate metabolism	hsa00030
Insulin signaling pathway	Endocrine system	hsa04910
GnRH signaling pathway	Endocrine system	hsa04912
Progesterone-mediated oocyte maturation	Endocrine system	hsa04914
Prolactin signaling pathway	Endocrine system	hsa04917
Ovarian steroidogenesis	Endocrine system	hsa04913
Platelet activation	Immune system	hsa04611
Antigen processing and presentation	Immune system	hsa04612
Toll-like receptor signaling pathway	Immune system	hsa04620
RIG-I-like receptor signaling pathway	Immune system	hsa04622
Fc epsilon RI signaling pathway	Immune system	hsa04664
Fc gamma R-mediated phagocytosis	Immune system	hsa04666
Leukocyte transendothelial migration	Immune system	hsa04670
Bacterial invasion of epithelial cells	Infectious disease	hsa05100
Vibrio cholerae infection	Infectious disease	hsa05110
Epithelial cell signaling in Helicobacter pylori inf	Infectious disease	hsa05120
Salmonella infection	Infectious disease	hsa05132
Pertussis	Infectious disease	hsa05133
Legionellosis	Infectious disease	hsa05134
Chagas disease (American trypanosomiasis)	Infectious disease	hsa05142
Amoebiasis	Infectious disease	hsa05146
Tuberculosis	Infectious disease	hsa05152
Hepatitis C	Infectious disease	hsa05160
Hepatitis B	Infectious disease	hsa05161
Glycerophospholipid metabolism	Other	hsa00564
Ribosome biogenesis in eukaryotes	Other	hsa03008
p53 signaling pathway	Other	hsa04115
Dorso-ventral axis formation	Other	hsa04320
Osteoclast differentiation	Other	hsa04380
Focal adhesion	Other	hsa04510
Adherens junction	Other	hsa04520
Synaptic vesicle cycle	Other	hsa04721
Regulation of actin cytoskeleton	Other	hsa04810
Amyotrophic lateral sclerosis (ALS)	Other	hsa05014
Alcoholism	Other	hsa05034
Primary immunodeficiency	Other	hsa05340
Vitamin digestion and absorption	Other	hsa04977
Morphine addiction	Other	hsa05032
MAPK signaling pathway	Signal transduction	hsa04010
ErbB signaling pathway	Signal transduction	hsa04012

Supplementary Table S2: This table contains the property of each node of the network. Degree of a node is the number of edges connected to a node. Betweenness centrality is a measure of how much information flows through a specific node, i.e., average number of shortest paths passing through the node. Degree refers to the number of neighbours of a node while betweenness centrality refers to how important the node is for maintaining the overall structure of that network. The two nodes with highest betweenness centrality (Glycolysis/Gluconeogenesis, Lysosome) in the network are highlighted.

KEGG Pathway Names	KEGG ID	Degree	Betweenness Centrality
Vitamin digestion and absorption	hsa04977	NA	NA
Ribosome biogenesis in eukaryotes	hsa03008	NA	NA
Glycolysis / Gluconeogenesis	hsa00010	26	1599.07
Lysosome	hsa04142	7	680.2
Insulin signaling pathway	hsa04910	89	560.44
Epithelial cell signaling in Helicobacter pylori infection	hsa05120	49	520.57
AMPK signaling pathway	hsa04152	62	520.28
Vibrio cholerae infection	hsa05110	37	439.59
Choline metabolism in cancer	hsa05231	90	433.04
Tuberculosis	hsa05152	87	410.94
Central carbon metabolism in cancer	hsa05230	81	403.15
Ovarian steroidogenesis	hsa04913	48	387.79
GnRH signaling pathway	hsa04912	107	383.52
Hepatitis B	hsa05161	106	347.57
Chagas disease (American trypanosomiasis)	hsa05142	104	328.8
HIF-1 signaling pathway	hsa04066	80	323.29
Fc epsilon RI signaling pathway	hsa04664	102	317.94
Pertussis	hsa05133	67	295.91
Progesterone-mediated oocyte maturation	hsa04914	103	287.93
Pathways in cancer	hsa05200	98	286.47
VEGF signaling pathway	hsa04370	103	265.42

Amoebiasis	hsa05146	99	248.79
Proteoglycans in cancer	hsa05205	100	230.53
FoxO signaling pathway	hsa04068	90	206.86
Phagosome	hsa04145	31	195.33
PI3K-Akt signaling pathway	hsa04151	80	176.5
Fc gamma R-mediated phagocytosis	hsa04666	83	170.39
MAPK signaling pathway	hsa04010	90	167.12
Platelet activation	hsa04611	100	166.21
Toll-like receptor signaling pathway	hsa04620	91	156.38
Rap1 signaling pathway	hsa04015	96	153.11
Morphine addiction	hsa05032	46	152.64
Prostate cancer	hsa05215	95	150.98
Glioma	hsa05214	97	145.97
TNF signaling pathway	hsa04668	91	136.56
Hepatitis C	hsa05160	91	131.46
Antigen processing and presentation	hsa04612	26	123.22
Bacterial invasion of epithelial cells	hsa05100	56	116.33
Pancreatic cancer	hsa05212	91	101.47
Osteoclast differentiation	hsa04380	87	97.12
Focal adhesion	hsa04510	80	90.01
Acute myeloid leukemia	hsa05221	84	78.81
Chemical carcinogenesis	hsa05204	14	75.3
Leukocyte transendothelial migration	hsa04670	66	72.24
Non-small cell lung cancer	hsa05223	86	64.38
Salmonella infection	hsa05132	48	61.81
Alcoholism	hsa05034	46	60.62
Regulation of actin cytoskeleton	hsa04810	62	60.6
Jak-STAT signaling pathway	hsa04630	61	58.74
Prolactin signaling pathway	hsa04917	91	57.33

Renal cell carcinoma	hsa05211	84	56.81
ErbB signaling pathway	hsa04012	91	56.53
Melanoma	hsa05218	81	45.43
Synaptic vesicle cycle	hsa04721	10	42.04
Galactose metabolism	hsa00052	8	41.96
Amyotrophic lateral sclerosis (ALS)	hsa05014	30	39.8
Glycerophospholipid metabolism	hsa00564	14	26.42
Bladder cancer	hsa05219	53	18.91
Adherens junction	hsa04520	27	17.54
RIG-I-like receptor signaling pathway	hsa04622	39	17.21
Legionellosis	hsa05134	27	9.08
Dorso-ventral axis formation	hsa04320	26	2
p53 signaling pathway	hsa04115	14	1.21
Transcriptional misregulation in cancer	hsa05202	6	0.78
Primary immunodeficiency	hsa05340	5	0.29
Pentose phosphate pathway	hsa00030	3	0

Supplementary Table S3: Three SLC cancers were selected for survival analysis. The value in each cell corresponds to the p-value for association of the pathway with the cancer type. At a threshold of p < 0.1, the cell has been high-lighted, noting significant association of the pathway with survival from cancer. Direction of pathway expression score was estimated from visual inspection of survival plot in the SLC cancers. For each cancer, proportion of pathways associated with survival was calculated and converted to percentage (bottom row of the table). For septic shock, pathway score was calculated in the survivor group compared to the non-survivor group, as described in the Methods. A direction of "High" was assigned, if the pathway was observed to be higher in the survivor group for four or more of the eight septic shock data sets tested. Otherwise, the direction of "Low" was assigned.

	P-value			Direction in Survivors			
	SLC group			SLC group			Septic Shock
Association with survival	**HNSC**	**KIRC**	**LIHC**	**HNSC**	**KIRC**	**LIHC**	
Glycolysis / Gluconeogenesis | hsa00010	0.07	0.84	0.24	Low	-	Low	High
Pentose phosphate pathway | hsa00030	0.81	0.74	0.26	-	-	Low	High
Galactose metabolism | hsa00052	0.99	0.61	0.99	-	High	-	High
Glycerophospholipid metabolism | hsa00564	0.63	0.65	0.88	-	-	-	High
Ribosome biogenesis in eukaryotes | hsa03008	0.26	0.40	0.62	High	-	-	High
MAPK signaling pathway | hsa04010	0.53	0.12	0.04	-	High	High	High
ErbB signaling pathway | hsa04012	0.08	0.08	0.22	High	High	-	High
Rap1 signaling pathway | hsa04015	0.51	0.03	0.01	-	High	High	High
HIF-1 signaling pathway | hsa04066	0.22	0.04	0.16	Low	High	-	High
FoxO signaling pathway | hsa04068	0.27	0.00	0.74	Low	High	-	High
p53 signaling pathway | hsa04115	0.50	0.24	0.44	-	High	-	Low
Lysosome | hsa04142	0.55	0.31	0.13	-	High	High	High
Phagosome | hsa04145	0.98	0.92	0.15	-	-	High	High
PI3K-Akt signaling pathway | hsa04151	0.88	0.15	0.00	-	High	High	High
AMPK signaling pathway | hsa04152	0.81	0.00	0.95	-	High	-	High

Pathway							
Dorso-ventral axis formation | hsa04320	0.01	0.01	0.04	High	High	High	High
VEGF signaling pathway | hsa04370	0.27	0.04	0.02	-	High	High	High
Osteoclast differentiation | hsa04380	0.88	0.21	0.08	-	High	High	High
Focal adhesion | hsa04510	0.77	0.12	0.00	-	High	High	High
Adherens junction | hsa04520	0.20	0.01	0.01	High	High	High	High
Platelet activation | hsa04611	0.96	0.10	0.00	-	High	High	High
Antigen processing and presentation | hsa04612	0.74	0.14	0.02	-	High	High	High
Toll-like receptor signaling pathway | hsa04620	0.85	0.17	0.55	-	High	High	High
RIG-I-like receptor signaling pathway | hsa04622	0.92	0.11	0.44	-	High	-	High
Jak-STAT signaling pathway | hsa04630	0.96	0.08	0.62	-	High	-	High
Fc epsilon RI signaling pathway | hsa04664	0.06	0.04	0.06	High	High	High	High
Fc gamma R-mediated phagocytosis | hsa04666	0.10	0.01	0.01	High	High	High	High
TNF signaling pathway | hsa04668	0.50	0.06	0.48	High	High	High	High
Leukocyte transendothelial migration | hsa04670	0.43	0.00	0.05	-	High	High	High
Synaptic vesicle cycle | hsa04721	0.78	0.97	0.11	-	-	High	High
Regulation of actin cytoskeleton | hsa04810	0.76	0.01	0.01	-	High	High	High
Insulin signaling pathway | hsa04910	0.72	0.01	0.47	-	High	High	High
GnRH signaling pathway | hsa04912	0.08	0.21	0.15	High	High	High	High
Ovarian steroidogenesis | hsa04913	0.99	0.02	0.80	-	High	-	High
Progesterone-mediated oocyte maturation | hsa04914	0.80	0.03	0.18	-	High	-	High
Prolactin signaling pathway | hsa04917	0.12	0.02	0.53	High	High	-	High
Vitamin digestion and absorption | hsa04977	0.84	0.35	0.97	-	Low	-	High
Amyotrophic lateral sclerosis (ALS) | hsa05014	0.14	0.11	0.26	-	High	High	High
Morphine addiction | hsa05032	0.20	0.28	0.02	-	High	High	High
Alcoholism | hsa05034	0.28	0.03	0.11	High	High	High	High
Bacterial invasion of epithelial cells | hsa05100	0.49	0.10	0.04	-	High	High	High
Vibrio cholerae infection | hsa05110	0.21	0.67	0.24	High	-	High	High

Pathway							
Epithelial cell signaling in Helicobacter pylori infection	hsa05120	0.12	0.21	0.57	High	High	High	High
Salmonella infection	hsa05132	0.07	0.55	0.38	High	-	High	High
Pertussis	hsa05133	0.98	0.50	0.39	-	-	High	High
Legionellosis	hsa05134	0.31	0.98	0.63	High	-	High	High
Chagas disease (American trypanosomiasis)	hsa05142	0.71	0.10	0.12	-	High	High	High
Amoebiasis	hsa05146	0.67	0.92	0.03	-	-	High	High
Tuberculosis	hsa05152	0.99	0.96	0.01	-	-	High	High
Hepatitis C	hsa05160	0.32	0.03	0.32	High	High	High	High
Hepatitis B	hsa05161	0.19	0.05	0.14	High	High	High	High
Pathways in cancer	hsa05200	0.67	0.01	0.01	-	High	High	High
Transcriptional misregulation in cancer	hsa05202	0.80	0.44	0.06	-	-	High	High
Chemical carcinogenesis	hsa05204	0.80	0.05	0.02	-	Low	Low	High
Proteoglycans in cancer	hsa05205	0.84	0.06	0.04	-	High	High	High
Renal cell carcinoma	hsa05211	0.60	0.04	0.08	-	High	High	High
Pancreatic cancer	hsa05212	0.45	0.01	0.28	High	High	High	High
Glioma	hsa05214	0.61	0.16	0.07	-	High	High	High
Prostate cancer	hsa05215	0.39	0.01	0.02	-	High	High	High
Melanoma	hsa05218	0.59	0.10	0.01	-	High	High	High
Bladder cancer	hsa05219	0.00	0.00	0.03	High	High	High	High
Acute myeloid leukemia	hsa05221	0.47	0.00	0.76	-	High	-	High
Non-small cell lung cancer	hsa05223	0.57	0.02	0.57	High	High	-	High
Central carbon metabolism in cancer	hsa05230	0.69	0.02	0.10	-	High	High	High
Choline metabolism in cancer	hsa05231	0.04	0.01	0.03	High	High	High	High
Primary immunodeficiency	hsa05340	0.77	0.22	0.31	-	High	High	High

Fraction of pathways associated with survival   0.14   0.52   0.42

Supplementary Table S4: List of additional cancer data sets for machine learning-based prediction of cancer samples.

GEO_ID	Cancer	Type of tumour	Number of samples	Number of tumour samples used in analysis	Number of control samples used in analysis	Platform	Normalization
GSE103512	Breast, Colorectal, Prostate, And Non-Small Cell Lung Cancer	Solid Tumor	280	242	38	GPL13158[HT_HG-U133_Plus_PM] Affymetrix HT HG-U133+ PM Array Plate	Quantile
GSE112790	Hepatocellular Carcinoma	Solid Tumor	198	183	15	GPL570 [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array	Quantile
GSE32665	Lung adenocarcinoma	Solid Tumor	170	85	85	GPL6102Illumina human-6 v2.0 expression beadchip	Quantile
GSE33479	Lung squamous carcinogenesis	Solid Tumor	122	14	27	GPL6480 Agilent-014850 Whole Human Genome Microarray 4x44K G4112F (Probe Name version)	Natural log of (Cy5/Cy3)
GSE84984	Colorectal Cancer	Solid Tumor	15	9	6	GPL17586 [HTA-2_0] Affymetrix Human Transcriptome Array 2.0 [transcript (gene) version]	RMA
GSE103236	Gastric Cancer	Solid Tumor	19	9	9	GPL4133Agilent-014850 Whole Human Genome Microarray 4x44K G4112F (Feature Number version)	Lowess

	Tang2013 [a]		Cao2016 [b]		Kazemina2015 [c] **	
Supplemental Table S5: Viral integration in TCGA samples. Results are derived from published data.						
	N (%)	P-value	N (%)	P-value	N (%)	P-value
Samples analysed in current manuscript	687		687		N.A.	
Overlap with published study	425 (61.9%)		533 (77.6%)		N.A.	
SLC samples	120 (28.2%)		200 (37.5%)		305	
CA samples	305 (71.8%)	3.00E-04	333 (62.5%)	1.00E-03	1175	4.10E-13
Viral integration in SLC	9 (7.5%)		60 (30%)		57 (18.7%)	
Viral integration in CA	2 (0.66 %)		58 (17.4 %)		66 (5.6%)	
					** Sample-level data are not available. Number and proportion of viral integration in SLC and CA samples are calculated from summary data provided in the publication (Table 1 of [c]).	

[a]   Tang KW, Alaei-Mahabadi B, Samuelsson T, Lindh M, Larsson E. The landscape of viral expression and host gene fusion and adaptation in human cancer. Nature Communications. 2013;4:1–9.

[b]   Cao S, Wendl MC, Wyczalkowski MA, Wylie K, Ye K, Jayasinghe R, et al. Divergent viral presentation among human tumors and adjacent normal tissues. Scientific Reports. 2016;6 June:1–12.

[c]   Kazemian M, Ren M, Lin J-X, Liao W, Spolski R, Leonard WJ. Possible Human Papillomavirus 38 Contamination of Endometrial Cancer RNA Sequencing Samples in The Cancer Genome Atlas Database. Journal of Virology. 2015;89:8967–73.

Additional text : Functional classification of the pathways

The selected 66 pathways are divided into categories based on their functional relevance. The categories include catabolism, immune system, infection, cancer, signal transduction, ribosome biogenesis and carbohydrate metabolism. Many of these pathways are related to immune response to infection, such as, clot formation, proinflammatory effects, antiviral effects, chemotactic effects and T cell stimulation, degranulation, cytokine gene transcription and generation of eicosanoids, phagocytosis, and migration of leukocytes to the site of injury, and are consistently up-regulated in both SS and SLC group.

Catabolism

Two catabolic pathways namely, Lysosome and Phagosome, are observed to be mostly up-regulated in SS and SLC (Fig. 2, Additional File 4: Table S1). Upon network analysis, it is revealed that lysosome pathway has a very high value for betweenness centrality (680.2) (Additional File 5: Table S2), thus being essential to the structure of the network. Likewise, Phagosome, another catabolic pathway linked to lysosome, is uniformly up regulated in SS and SLC groups (Additional File 2: Figure S2).

Muscle wasting is one of the most common phenomena in both SS and cancer. Lysosome mediated protein degradation has been noted on a substantial scale in such cases. Further, transcriptome based meta-analysis conducted by Ma et al., reported up-regulation of lysosome pathway in sepsis while increased biogenesis of lysosomes has been observed in cancer cells. In this study, we observe consistent up-regulation of catabolic pathways associated with lysosome and phagosome in SS and SLC, suggesting high catabolic rate in both the groups. Besides, lysosome is now considered a hub of metabolic signalling given its key role in maintaining cellular homeostasis. It also appears as a central node in our network with high betweenness centrality.

Immune system

Both cancer and septic shock are associated with dysregulation in immune function. It is observed that immune system pathways associated with clot formation (Platelet activation), proinflammatory effects, antiviral effects, chemotactic effects and T cell stimulation (Toll-like receptor signalling pathway), degranulation, cytokine gene transcription and generation of eicosanoids (Fc epsilon RI signalling pathway), phagocytosis (Fc gamma R-mediated phagocytosis), and migration of leukocytes to the site of injury (Leukocyte transendothelial migration) are uniformly up regulated in both SS and SLC groups (Additional File 2: Figure S2).

Infection

Infection is a common theme in both septic shock (which originates as sepsis) and many cancers (known to be induced by microbial infection). Many infection-associated pathways, such as, Bacterial invasion of epithelial cells, Vibrio cholerae infection, Epithelial cell signalling in Helicobacter pylori infection, Salmonella infection, Pertussis, Legionellosis, Tuberculosis, Chagas disease (American trypanosomiasis), Amoebiasis, Hepatitis C and Hepatitis B are significantly up regulated in SS and SLC group (Additional File 2: Figure S2).

Cancer pathways

Many cancer-associated pathways, such as Transcriptional misregulation in cancer, Proteoglycans in cancer, Central carbon metabolism in cancer, Choline metabolism in cancer, Chemical carcinogenesis, Renal cell carcinoma, Pancreatic cancer, Glioma, Prostate cancer, Melanoma, Bladder cancer, Acute myeloid leukemia, Non-small cell lung cancer are up regulated in SS and SLC group (Additional File 2: Figure S2).

Signal transduction

Signal transduction pathways involved in cell proliferation, differentiation, adhesion, migration, survival, cell cycle progression, anti-apoptosis (MAPK, ErbB, Rap1, VEGF, JAK-STAT and PI3k-Akt signalling pathways) and cell cycle regulation, apoptosis, autophagy, oxidative stress response, DNA repair, immune regulation, muscle atrophy, growth arrest, leukocyte recruitment and activation, synthesis of inflammatory mediators, remodelling of extracellular matrix (HIF1, AMPK, FoxO and TNF signalling pathways) are uniformly up-regulated in SS group, and in most of the SLC group (Additional File 2: Figure S2).

Endocrine system

Five pathways associated with endocrine system viz., Insulin signalling, GnRH signalling, Progesterone-mediated oocyte maturation, Prolactin signalling pathway and Ovarian steroidogenesis are up-regulated in all SS groups as well as in SLC group (Additional File 2: Figure S2).

Carbohydrate metabolism

Carbohydrate metabolism pathways including Galactose metabolism, Glycolysis/Gluconeogenesis, and Pentose phosphate pathway are up-regulated in SS group and most of the SLC group cancers. In our study, Galactose metabolism pathway is up-regulated in SLC and SS groups. Glycolysis/Gluconeogenesis (a source of energy and metabolite precursors of other pathways) plays a central role in cell as reflected by highest betweenness centrality parameter value i.e. 1599.06 (Additional File 5: Table S2). Pentose phosphate pathway, which generates precursors for synthesis of purine, pyrimidine and histidine, is up-regulated across the SS group along with the LIHC, CHOL, ESCA and STAD of SLC group.

Gene–level heatmap for 66 pathways

Chemical carcinogenesis
hsa05204

	CA	SLC	SS	
				ADH1B | alcohol dehydrogenase 1B (class I), beta polypeptide
				ALDH3B1 | aldehyde dehydrogenase 3 family member B1
				MGST3 | microsomal glutathione S−transferase 3
				ADH5 | alcohol dehydrogenase 5 (class III), chi polypeptide
				GSTM2 | glutathione S−transferase mu 2
				ARNT | aryl hydrocarbon receptor nuclear translocator
				KYAT1 | kynurenine aminotransferase 1
				GSTO1 | glutathione S−transferase omega 1
				GSTK1 | glutathione S−transferase kappa 1
				UGT2B17 | UDP glucuronosyltransferase family 2 member B17
				UGT1A8 | UDP glucuronosyltransferase family 1 member A8
				ALDH1A3 | aldehyde dehydrogenase 1 family member A3
				GSTO2 | glutathione S−transferase omega 2
				KYAT3 | kynurenine aminotransferase 3
				GSTM1 | glutathione S−transferase mu 1
				UGT2B28 | UDP glucuronosyltransferase family 2 member B28
				CYP1A2 | cytochrome P450 family 1 subfamily A member 2
				GSTA1 | glutathione S−transferase alpha 1
				GSTA4 | glutathione S−transferase alpha 4
				ADH1A | alcohol dehydrogenase 1A (class I), alpha polypeptide
				CYP2E1 | cytochrome P450 family 2 subfamily E member 1
				ALDH3B2 | aldehyde dehydrogenase 3 family member B2
				SULT2A1 | sulfotransferase family 2A member 1

Cancer

**Bladder cancer
hsa05219**

TYMP | thymidine phosphorylase
MMP9 | matrix metallopeptidase 9
MMP2 | matrix metallopeptidase 2
MAPK3 | mitogen−activated protein kinase 3
RB1 | RB transcriptional corepressor 1
VEGFA | vascular endothelial growth factor A
DAPK3 | death associated protein kinase 3
NRAS | NRAS proto−oncogene, GTPase
CDKN2A | cyclin dependent kinase inhibitor 2A
THBS1 | thrombospondin 1
EGFR | epidermal growth factor receptor
ARAF | A−Raf proto−oncogene, serine/threonine kinase
E2F1 | E2F transcription factor 1
MAPK1 | mitogen−activated protein kinase 1
FGFR3 | fibroblast growth factor receptor 3
DAPK2 | death associated protein kinase 2
MDM2 | MDM2 proto−oncogene
E2F2 | E2F transcription factor 2
E2F3 | E2F transcription factor 3
MAP2K1 | mitogen−activated protein kinase kinase 1
MAP2K2 | mitogen−activated protein kinase kinase 2
EGF | epidermal growth factor
RPS6KA5 | ribosomal protein S6 kinase A5
ERBB2 | erb−b2 receptor tyrosine kinase 2
KRAS | KRAS proto−oncogene, GTPase
BRAF | B−Raf proto−oncogene, serine/threonine kinase
MMP1 | matrix metallopeptidase 1

CA SLC SS

Cancer

Color Key and Histogran

Pathways in cancer
hsa05200

COL4A2 | collagen type IV alpha 2 chain

CA   SLC   SS

Cancer

Transcriptional misregulation in cancer
hsa05202

ERG | ERG, ETS transcription factor
MEIS1 | Meis homeobox 1
TGFBR2 | transforming growth factor beta receptor 2
MMP9 | matrix metallopeptidase 9
RARA | retinoic acid receptor alpha
ZBTB16 | zinc finger and BTB domain containing 16
CBX3 | chromobox homolog 3
CDKN2C | cyclin-dependent kinase inhibitor 2C
PROM1 | prominin 1
FLT1 | fms related tyrosine kinase 1
LMO2 | LIM domain only 2
EBF3 | early B-cell factor 3
ETV1 | ets variant 1
REL | v-rel avian reticuloendotheliosis viral oncogene homolog
ELL | elongation factor RNA polymerase II
FLI1 | Fli-1 proto-oncogene, ETS transcription factor
PPARG | peroxisome proliferator-activated receptor gamma
BCL3 | B-cell CLL/lymphoma 3
TCF3 | transcription factor binding to IGHM enhancer 3
HOXA11 | homeobox A11
PML | promyelocytic leukemia
SIX1 | SIX homeobox 1
ITGAM | integrin subunit alpha M
CEBPA | CCAAT/enhancer binding protein alpha
SPI1 | Spi-1 proto-oncogene
MLF1 | myeloid leukemia factor 1
NFKB1 | nuclear factor kappa B subunit 1
ARNT2 | aryl hydrocarbon receptor nuclear translocator 2
CDK14 | cyclin dependent kinase 14
MET | MET proto-oncogene, receptor tyrosine kinase
PAX8 | paired box 8
ID2 | inhibitor of DNA binding 2
MMP3 | matrix metallopeptidase 3
CDK9 | cyclin dependent kinase 9
DOT1L | DOT1 like histone lysine methyltransferase
RELA | RELA proto-oncogene, NF-kB subunit
FUS | FUS RNA binding protein
RXRG | retinoid X receptor gamma
EWSR1 | EWS RNA binding protein 1
SMARCB1 | SWI/SNF related, matrix associated, actin dependent regulator
MLLT3 | myeloid/lymphoid or mixed-lineage leukemia; translocated to, 3
KMT2C | lysine methyltransferase 2C
SSX1 | SSX family member 1
KDM6A | lysine demethylase 6A
WHSC1L1 | Wolf-Hirschhorn syndrome candidate 1-like 1
ELL | elongation factor RNA polymerase II
MLLT1 | myeloid/lymphoid or mixed-lineage leukemia; translocated to, 1
AFF1 | AF4/FMR2 family member 1
TAF15 | TATA-box binding protein associated factor 15
SETD2 | SET domain containing 2
FOXO1 | forkhead box O1
SMAD1 | SMAD family member 1
MYB | MYB proto-oncogene, transcription factor
MAF | MAF bZIP transcription factor
DUSP6 | dual specificity phosphatase 6
BCL6 | B-cell CLL/lymphoma 6
RUNX1 | runt related transcription factor 1
KLF5 | Kruppel like factor 5
RXRB | retinoid X receptor beta
IL1R1 | interleukin 1 receptor type 1
FCGR1A | Fc fragment of IgG receptor Ia
GADD45B | growth arrest and DNA damage inducible beta
DDIT3 | DNA damage inducible transcript 3
PRCC | papillary renal cell carcinoma (translocation-associated)
NR4A3 | nuclear receptor subfamily 4 group A member 3
ZBTB17 | zinc finger and BTB domain containing 17
REL | v-rel avian reticuloendotheliosis viral oncogene homolog
RELB | RELB proto-oncogene, NF-kB subunit
MDM2 | MDM2 proto-oncogene
HIST3H3 | histone cluster 3, H3
HIST1H3A | histone cluster 1, H3 family member a
FLT3 | fms related tyrosine kinase 3
LDB1 | LIM domain binding 1
NGFR | nerve growth factor receptor
HIST1H4H | histone cluster 1, H4 family member h
PLAU | plasminogen activator, urokinase
MPO | myeloperoxidase
MMP1 | matrix metallopeptidase 1
BMI1 | BMI1 proto-oncogene, polycomb ring finger
PIM2 | Pim-2 proto-oncogene, serine/threonine kinase
HMX1 | H6 family homeobox 1
SIX4 | SIX homeobox 4
CEBPE | CCAAT/enhancer binding protein epsilon
IL3 | interleukin 3
SIX3 | SIX homeobox 3
HIST2H3A | histone cluster 2, H3 family member a
HIST1H3E | histone cluster 1, H3 family member e
WNT16 | wnt family member 16
RMND5A | required for meiotic nuclear division 5 homolog A
TSPYL2 | TSPY like 2
HMGA2 | high mobility group AT-hook 2
SPINT1 | serine peptidase inhibitor, Kunitz type 1
MYCN | v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog
NKX3-1 | NK3 homeobox 1
SIX4 | SIX homeobox 4

CA   SLC   SS

Cancer

Color Key and Histogran

Count

**Proteoglycans in cancer
hsa05205**

ITGA5 | integrin subunit alpha 5
DCN | decorin
GPC3 | glypican 3
TGFB1 | transforming growth factor beta 1
MMP9 | matrix metallopeptidase 9
TFAP2 | transcription factor AP-2 beta (activating enhancer binding protein 2 beta)
TLR4 | toll like receptor 4
PRKCB | protein kinase C beta
CD44 | CD44 molecule (Indian blood group)
MAPK8 | mitogen-activated protein kinase 8
FLT4 | fms related tyrosine kinase 4
TLR2 | toll like receptor 2
ITPR3 | inositol 1,4,5-trisphosphate receptor type 3
PIK3CD | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
GRB2 | growth factor receptor bound protein 2
PPP1CC | protein phosphatase 1 catalytic subunit gamma
PLCG1 | phospholipase C gamma 1
FLT1 | fms related tyrosine kinase 1
PDGFRA | platelet derived growth factor receptor alpha
HSPG2 | heparan sulfate proteoglycan 2
CAMK2G | calcium/calmodulin dependent protein kinase II gamma
SDC2 | syndecan 2
PTPN6 | protein tyrosine phosphatase, non-receptor type 6
VEGFA | vascular endothelial growth factor A
COL21A1 | collagen type XXI alpha 1 chain
WNT5A | Wnt family member 5A
MAPK11 | mitogen-activated protein kinase 11
HOXD10 | homeobox D10
ROCK1 | Rho associated coiled-coil containing protein kinase 1
FAS | Fas cell surface death receptor
PPP1R12A | protein phosphatase 1 regulatory subunit 12A
PIK3CB | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta
TIMP3 | TIMP metallopeptidase inhibitor 3
IGF1 | insulin like growth factor 1
TIAM1 | T cell lymphoma invasion and metastasis 1
MET | MET proto-oncogene, receptor tyrosine kinase
SDC4 | syndecan 4
ANK2 | ankyrin 2
CBL | Cbl proto-oncogene
SRC | SRC proto-oncogene, non-receptor tyrosine kinase
PIK3CA | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
RHOA | ras homolog family member A
ERBB2 | erb-b2 receptor tyrosine kinase 2
PTPN11 | protein tyrosine phosphatase, non-receptor type 11
ESR1 | estrogen receptor 1
PIK3CG | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma
GPC1 | glypican 1
MAPK1 | mitogen-activated protein kinase 1
STAT3 | signal transducer and activator of transcription 3
TWIST1 | twist family bHLH transcription factor 1
VAV2 | vav guanine nucleotide exchange factor 2
ARHGEF12 | Rho guanine nucleotide exchange factor 12
PIK3CA | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PRKCA | protein kinase C alpha
MAPK14 | mitogen-activated protein kinase 14
CASP3 | caspase 3, apoptosis-related cysteine peptidase
PRKACB | protein kinase cAMP-activated catalytic subunit beta
MAPK12 | mitogen-activated protein kinase 12
MAPK13 | mitogen-activated protein kinase 13
RDX | radixin
TFAP2A | transcription factor AP-2 alpha
ERBB4 | erb-b2 receptor tyrosine kinase 4
AKT3 | AKT serine/threonine kinase 3
MAPK9 | mitogen-activated protein kinase 9
PRKCG | protein kinase C gamma
HRAS | HRas proto-oncogene, GTPase
RPS6KB2 | ribosomal protein S6 kinase B2
PRKAG2 | protein kinase AMP-activated catalytic subunit gamma 2
ROCK2 | Rho associated coiled-coil containing protein kinase 2
PLAUR | plasminogen activator, urokinase receptor
SLC9A1 | solute carrier family 9 member A1
MMP2 | matrix metallopeptidase 2
TIAM2 | T cell lymphoma invasion and metastasis 2
PPP1R12B | protein phosphatase 1 regulatory subunit 12B
WNT16 | Wnt family member 16
FZD3 | frizzled class receptor 3

CA
SLC
SS

Cancer

**Color Key
and Histogram**

Count

−1.5 0 1

Value

Renal cell carcinoma
hsa05211

EPAS1 | endothelial PAS domain protein 1
TGFB1 | transforming growth factor beta 1
PDGFB | platelet derived growth factor subunit B
MAPK3 | mitogen−activated protein kinase 3
TGFA | transforming growth factor alpha
PIK3CD | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit delta
GRB2 | growth factor receptor bound protein 2
TGFB2 | transforming growth factor beta 2
RAP1A | RAP1A, member of RAS oncogene family
HIF1A | hypoxia inducible factor 1 alpha subunit
PAK1 | p21 (RAC1) activated kinase 1
VEGFA | vascular endothelial growth factor A
ARNT2 | aryl hydrocarbon receptor nuclear translocator 2
NRAS | NRAS proto−oncogene, GTPase
PIK3CB | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit beta
SLC2A1 | solute carrier family 2 member 1
PIK3R5 | phosphoinositide−3−kinase regulatory subunit 5
CRK | CRK proto−oncogene, adaptor protein
TGFB3 | transforming growth factor beta 3
MET | MET proto−oncogene, receptor tyrosine kinase
EGLN2 | egl−9 family hypoxia inducible factor 2
EGLN3 | egl−9 family hypoxia inducible factor 3
GAB1 | GRB2 associated binding protein 1
CDC42 | cell division cycle 42
FLCN | folliculin
EP300 | E1A binding protein p300
RAC1 | Rac family small GTPase 1
PAK2 | p21 (RAC1) activated kinase 2
ARNT | aryl hydrocarbon receptor nuclear translocator
ARAF | A−Raf proto−oncogene, serine/threonine kinase
PIK3CG | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit gamma
MAPK1 | mitogen−activated protein kinase 1
EGLN1 | egl−9 family hypoxia inducible factor 1
SOS1 | SOS Ras/Rac guanine nucleotide exchange factor 1
RBX1 | ring−box 1
PIK3CA | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit alpha
PAK3 | p21 (RAC1) activated kinase 3
CREBBP | CREB binding protein
MAP2K1 | mitogen−activated protein kinase kinase 1
MAP2K2 | mitogen−activated protein kinase kinase 2
VHL | von Hippel−Lindau tumor suppressor
KRAS | KRAS proto−oncogene, GTPase
BRAF | B−Raf proto−oncogene, serine/threonine kinase
ELOC | elongin C
ELOB | elongin B
PIK3R2 | phosphoinositide−3−kinase regulatory subunit 2

CA   SLC   SS

Cancer

**Color Key
and Histogram**

Count

−1   1

Value

**Pancreatic cancer
hsa05212**

RAC2 | Rac family small GTPase 2
TGFB1 | transforming growth factor beta 1
TGFBR2 | transforming growth factor beta receptor 2
MAPK3 | mitogen−activated protein kinase 3
STAT1 | signal transducer and activator of transcription 1
TGFA | transforming growth factor alpha
PIK3CD | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit delta
TGFB2 | transforming growth factor beta 2
RALB | RAS like proto−oncogene B
RB1 | RB transcriptional corepressor 1
VEGFA | vascular endothelial growth factor A
RAD51 | RAD51 recombinase
NFKB1 | nuclear factor kappa B subunit 1
JAK1 | Janus kinase 1
PIK3CB | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit beta
PIK3R5 | phosphoinositide−3−kinase regulatory subunit 5
CDKN2A | cyclin dependent kinase inhibitor 2A
TGFB3 | transforming growth factor beta 3
CDC42 | cell division cycle 42
RALBP1 | ralA binding protein 1
TGFBR1 | transforming growth factor beta receptor 1
RELA | RELA proto−oncogene, NF−kB subunit
CHUK | conserved helix−loop−helix ubiquitous kinase
RAC1 | Rac family small GTPase 1
EGFR | epidermal growth factor receptor
BCL2L1 | BCL2 like 1
ARAF | A−Raf proto−oncogene, serine/threonine kinase
PIK3CG | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit gamma
E2F1 | E2F transcription factor 1
IKBKG | inhibitor of nuclear factor kappa B kinase subunit gamma
MAPK1 | mitogen−activated protein kinase 1
STAT3 | signal transducer and activator of transcription 3
BAD | BCL2 associated agonist of cell death
PLD1 | phospholipase D1
PIK3CA | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit alpha
SMAD4 | SMAD family member 4
E2F2 | E2F transcription factor 2
E2F3 | E2F transcription factor 3
MAP2K1 | mitogen−activated protein kinase kinase 1
EGF | epidermal growth factor
ERBB2 | erb−b2 receptor tyrosine kinase 2
KRAS | KRAS proto−oncogene, GTPase
BRAF | B−Raf proto−oncogene, serine/threonine kinase
BRCA2 | BRCA2, DNA repair associated
PIK3R2 | phosphoinositide−3−kinase regulatory subunit 2
RAC3 | Rac family small GTPase 3

CA   SLC   SS

Cancer

**Color Key
and Histogran**

**Glioma
hsa05214**

PDGFB | platelet derived growth factor subunit B
PRKCB | protein kinase C beta
MAPK3 | mitogen−activated protein kinase 3
SHC1 | SHC adaptor protein 1
TGFA | transforming growth factor alpha
PIK3CD | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit delta
GRB2 | growth factor receptor bound protein 2
PLCG2 | phospholipase C gamma 2
CAMK2G | calcium/calmodulin dependent protein kinase II gamma
RB1 | RB transcriptional corepressor 1
NRAS | NRAS proto−oncogene, GTPase
PIK3CB | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit beta
PIK3R5 | phosphoinositide−3−kinase regulatory subunit 5
CDKN2A | cyclin dependent kinase inhibitor 2A
EGFR | epidermal growth factor receptor
ARAF | A−Raf proto−oncogene, serine/threonine kinase
PIK3CG | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit gamma
PTEN | phosphatase and tensin homolog
E2F1 | E2F transcription factor 1
MAPK1 | mitogen−activated protein kinase 1
SOS1 | SOS Ras/Rac guanine nucleotide exchange factor 1
PIK3CA | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit alpha
MDM2 | MDM2 proto−oncogene
E2F2 | E2F transcription factor 2
SHC3 | SHC adaptor protein 3
E2F3 | E2F transcription factor 3
MAP2K1 | mitogen−activated protein kinase kinase 1
MAP2K2 | mitogen−activated protein kinase kinase 2
EGF | epidermal growth factor
SHC2 | SHC adaptor protein 2
SHC4 | SHC adaptor protein 4
PRKCG | protein kinase C gamma
KRAS | KRAS proto−oncogene, GTPase
BRAF | B−Raf proto−oncogene, serine/threonine kinase
PIK3R2 | phosphoinositide−3−kinase regulatory subunit 2
CALML3 | calmodulin like 3

CA

SLC

SS

Cancer

Color Key and Histogram

Count

0 6

−1   1

Value

Prostate cancer
hsa05215

TCF7L1 | transcription factor 7 like 1
PDGFB | platelet derived growth factor subunit B
NFKBIA | NFKB inhibitor alpha
MAPK3 | mitogen−activated protein kinase 3
TGFA | transforming growth factor alpha
BCL2 | BCL2, apoptosis regulator
PIK3CD | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit delta
CTNNB1 | catenin beta 1
GRB2 | growth factor receptor bound protein 2
TCF7L2 | transcription factor 7 like 2
RB1 | RB transcriptional corepressor 1
NFKB1 | nuclear factor kappa B subunit 1
NRAS | NRAS proto−oncogene, GTPase
PIK3CB | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit beta
PIK3R5 | phosphoinositide−3−kinase regulatory subunit 5
CREB3 | cAMP responsive element binding protein 3
CREB3L2 | cAMP responsive element binding protein 3 like 2
RELA | RELA proto−oncogene, NF−kB subunit
EP300 | E1A binding protein p300
CHUK | conserved helix−loop−helix ubiquitous kinase
EGFR | epidermal growth factor receptor
ARAF | A−Raf proto−oncogene, serine/threonine kinase
PIK3CG | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit gamma
PTEN | phosphatase and tensin homolog
E2F1 | E2F transcription factor 1
IKBKG | inhibitor of nuclear factor kappa B kinase subunit gamma
FOXO1 | forkhead box O1
MAPK1 | mitogen−activated protein kinase 1
SOS1 | SOS Ras/Rac guanine nucleotide exchange factor 1
BAD | BCL2 associated agonist of cell death
CCNE1 | cyclin E1
CDK2 | cyclin dependent kinase 2
PIK3CA | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit alpha
CREB5 | cAMP responsive element binding protein 5
MDM2 | MDM2 proto−oncogene
E2F2 | E2F transcription factor 2
GSK3B | glycogen synthase kinase 3 beta
PDPK1 | 3−phosphoinositide dependent protein kinase 1
CREBBP | CREB binding protein
E2F3 | E2F transcription factor 3
MAP2K1 | mitogen−activated protein kinase kinase 1
MAP2K2 | mitogen−activated protein kinase kinase 2
EGF | epidermal growth factor
PDGFC | platelet derived growth factor C
ERBB2 | erb−b2 receptor tyrosine kinase 2
CCNE2 | cyclin E2
KRAS | KRAS proto−oncogene, GTPase
BRAF | B−Raf proto−oncogene, serine/threonine kinase
PIK3R2 | phosphoinositide−3−kinase regulatory subunit 2

CA   SLC   SS

Cancer

**Color Key
and Histogram**

Count

0 15

−1 1

Value

Melanoma
hsa05218

PDGFB | platelet derived growth factor subunit B
MAPK3 | mitogen−activated protein kinase 3
PIK3CD | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit delta
RB1 | RB transcriptional corepressor 1
NRAS | NRAS proto−oncogene, GTPase
PIK3CB | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit beta
PIK3R5 | phosphoinositide−3−kinase regulatory subunit 5
CDKN2A | cyclin dependent kinase inhibitor 2A
MET | MET proto−oncogene, receptor tyrosine kinase
EGFR | epidermal growth factor receptor
ARAF | A−Raf proto−oncogene, serine/threonine kinase
PIK3CG | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit gamma
PTEN | phosphatase and tensin homolog
E2F1 | E2F transcription factor 1
MAPK1 | mitogen−activated protein kinase 1
BAD | BCL2 associated agonist of cell death
PIK3CA | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit alpha
FGF1 | fibroblast growth factor 1
MDM2 | MDM2 proto−oncogene
E2F2 | E2F transcription factor 2
E2F3 | E2F transcription factor 3
FGF9 | fibroblast growth factor 9
MAP2K1 | mitogen−activated protein kinase kinase 1
MAP2K2 | mitogen−activated protein kinase kinase 2
FGF12 | fibroblast growth factor 12
EGF | epidermal growth factor
PDGFC | platelet derived growth factor C
FGF11 | fibroblast growth factor 11
FGF19 | fibroblast growth factor 19
KRAS | KRAS proto−oncogene, GTPase
FGF14 | fibroblast growth factor 14
FGF22 | fibroblast growth factor 22
FGF20 | fibroblast growth factor 20
FGF17 | fibroblast growth factor 17
FGF6 | fibroblast growth factor 6
FGF4 | fibroblast growth factor 4
BRAF | B−Raf proto−oncogene, serine/threonine kinase
FGF5 | fibroblast growth factor 5
PIK3R2 | phosphoinositide−3−kinase regulatory subunit 2

CA SLC SS

Cancer

Color Key
and Histogran

Count

0   4

−1   0   1

Value

Acute myeloid leukemia
hsa05221

TCF7L1 | transcription factor 7 like 1
RARA | retinoic acid receptor alpha
MAPK3 | mitogen−activated protein kinase 3
STAT5A | signal transducer and activator of transcription 5A
PIK3CD | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit delta
PML | promyelocytic leukemia
GRB2 | growth factor receptor bound protein 2
SPI1 | Spi−1 proto−oncogene
TCF7L2 | transcription factor 7 like 2
CEBPA | CCAAT/enhancer binding protein alpha
NFKB1 | nuclear factor kappa B subunit 1
STAT5B | signal transducer and activator of transcription 5B
NRAS | NRAS proto−oncogene, GTPase
PIK3CB | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit beta
PIK3R5 | phosphoinositide−3−kinase regulatory subunit 5
RELA | RELA proto−oncogene, NF−kB subunit
CHUK | conserved helix−loop−helix ubiquitous kinase
ARAF | A−Raf proto−oncogene, serine/threonine kinase
PIK3CG | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit gamm
IKBKG | inhibitor of nuclear factor kappa B kinase subunit gamma
MAPK1 | mitogen−activated protein kinase 1
STAT3 | signal transducer and activator of transcription 3
SOS1 | SOS Ras/Rac guanine nucleotide exchange factor 1
BAD | BCL2 associated agonist of cell death
KIT | KIT proto−oncogene receptor tyrosine kinase
PIK3CA | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit alpha
FLT3 | fms related tyrosine kinase 3
MAP2K1 | mitogen−activated protein kinase kinase 1
MAP2K2 | mitogen−activated protein kinase kinase 2
CCNA1 | cyclin A1
KRAS | KRAS proto−oncogene, GTPase
RPS6KB2 | ribosomal protein S6 kinase B2
BRAF | B−Raf proto−oncogene, serine/threonine kinase
PIK3R2 | phosphoinositide−3−kinase regulatory subunit 2
EIF4EBP1 | eukaryotic translation initiation factor 4E binding protein 1

CA   SLC   SS

Cancer

**Color Key
and Histogran**

**Non−small cell lung cancer
hsa05223**

PRKCB | protein kinase C beta
MAPK3 | mitogen−activated protein kinase 3
TGFA | transforming growth factor alpha
PIK3CD | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit delta
GRB2 | growth factor receptor bound protein 2
PLCG2 | phospholipase C gamma 2
RB1 | RB transcriptional corepressor 1
NRAS | NRAS proto−oncogene, GTPase
PIK3CB | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit beta
PIK3R5 | phosphoinositide−3−kinase regulatory subunit 5
STK4 | serine/threonine kinase 4
CDKN2A | cyclin dependent kinase inhibitor 2A
RASSF5 | Ras association domain family member 5
RXRG | retinoid X receptor gamma
EGFR | epidermal growth factor receptor
ARAF | A−Raf proto−oncogene, serine/threonine kinase
PIK3CG | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit gamm
E2F1 | E2F transcription factor 1
MAPK1 | mitogen−activated protein kinase 1
FOXO3 | forkhead box O3
RXRB | retinoid X receptor beta
SOS1 | SOS Ras/Rac guanine nucleotide exchange factor 1
BAD | BCL2 associated agonist of cell death
PIK3CA | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit alpha
E2F2 | E2F transcription factor 2
PDPK1 | 3−phosphoinositide dependent protein kinase 1
E2F3 | E2F transcription factor 3
MAP2K1 | mitogen−activated protein kinase kinase 1
MAP2K2 | mitogen−activated protein kinase kinase 2
EGF | epidermal growth factor
EML4 | echinoderm microtubule associated protein like 4
ERBB2 | erb−b2 receptor tyrosine kinase 2
PRKCG | protein kinase C gamma
KRAS | KRAS proto−oncogene, GTPase
BRAF | B−Raf proto−oncogene, serine/threonine kinase
ALK | ALK receptor tyrosine kinase
PIK3R2 | phosphoinositide−3−kinase regulatory subunit 2
FHIT | fragile histidine triad

CA SLC SS

Cancer

**Color Key
and Histogram**

Count

−1.5 0 1

Value

Central carbon metabolism in cancer
hsa05230

HKDC1 | hexokinase domain containing 1
MAPK3 | mitogen−activated protein kinase 3
PIK3CD | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit delta
HIF1A | hypoxia inducible factor 1 alpha subunit
SLC1A5 | solute carrier family 1 member 5
SLC16A3 | solute carrier family 16 member 3
NRAS | NRAS proto−oncogene, GTPase
PIK3CB | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit beta
SLC2A1 | solute carrier family 2 member 1
HK2 | hexokinase 2
PIK3R5 | phosphoinositide−3−kinase regulatory subunit 5
MET | MET proto−oncogene, receptor tyrosine kinase
EGFR | epidermal growth factor receptor
SIRT6 | sirtuin 6
PIK3CG | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit gamma
PTEN | phosphatase and tensin homolog
G6PD | glucose−6−phosphate dehydrogenase
TIGAR | TP53 induced glycolysis regulatory phosphatase
MAPK1 | mitogen−activated protein kinase 1
FGFR3 | fibroblast growth factor receptor 3
HK3 | hexokinase 3
KIT | KIT proto−oncogene receptor tyrosine kinase
PIK3CA | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit alpha
PKM | pyruvate kinase M1/2
SCO2 | SCO2, cytochrome c oxidase assembly protein
FLT3 | fms related tyrosine kinase 3
PGAM1 | phosphoglycerate mutase 1
MAP2K1 | mitogen−activated protein kinase kinase 1
MAP2K2 | mitogen−activated protein kinase kinase 2
NTRK3 | neurotrophic receptor tyrosine kinase 3
PFKM | phosphofructokinase, muscle
SIRT3 | sirtuin 3
ERBB2 | erb−b2 receptor tyrosine kinase 2
LDHA | lactate dehydrogenase A
KRAS | KRAS proto−oncogene, GTPase
IDH1 | isocitrate dehydrogenase (NADP(+)) 1, cytosolic
PIK3R2 | phosphoinositide−3−kinase regulatory subunit 2
PDHA1 | pyruvate dehydrogenase E1 alpha 1 subunit
PDHB | pyruvate dehydrogenase E1 beta subunit
GLS2 | glutaminase 2
SLC7A5 | solute carrier family 7 member 5

CA   SLC   SS

Cancer

**Color Key
and Histogran**

Count

−1.5 0 1
Value

Choline metabolism in cancer
hsa05231

RAC2 | Rac family small GTPase 2
SLC44A4 | solute carrier family 44 member 4
PDGFB | platelet derived growth factor subunit B
PRKCB | protein kinase C beta
SLC22A4 | solute carrier family 22 member 4
MAPK3 | mitogen−activated protein kinase 3
PIP5K1B | phosphatidylinositol−4−phosphate 5−kinase type 1 beta
PLA2G4A | phospholipase A2 group IVA
SLC44A1 | solute carrier family 44 member 1
PIK3CD | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit delta
GRB2 | growth factor receptor bound protein 2
HIF1A | hypoxia inducible factor 1 alpha subunit
CHKA | choline kinase alpha
NRAS | NRAS proto−oncogene, GTPase
WASF2 | WAS protein family member 2
WAS | Wiskott−Aldrich syndrome
PIK3CB | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit beta
PIK3R5 | phosphoinositide−3−kinase regulatory subunit 5
SLC44A3 | solute carrier family 44 member 3
GPCPD1 | glycerophosphocholine phosphodiesterase 1
PCYT1A | phosphate cytidylyltransferase 1, choline, alpha
SLC44A5 | solute carrier family 44 member 5
RHEB | Ras homolog, mTORC1 binding
RAC1 | Rac family small GTPase 1
EGFR | epidermal growth factor receptor
DGKH | diacylglycerol kinase eta
PIK3CG | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit gamma
SP1 | Sp1 transcription factor
MAPK1 | mitogen−activated protein kinase 1
PLD2 | phospholipase D2
SOS1 | SOS Ras/Rac guanine nucleotide exchange factor 1
PLD1 | phospholipase D1
PIP5K1A | phosphatidylinositol−4−phosphate 5−kinase type 1 alpha
PIK3CA | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit alpha
DGKG | diacylglycerol kinase gamma
PDPK1 | 3−phosphoinositide dependent protein kinase 1
MAP2K1 | mitogen−activated protein kinase kinase 1
MAP2K2 | mitogen−activated protein kinase kinase 2
EGF | epidermal growth factor
WASL | Wiskott−Aldrich syndrome like
SLC22A5 | solute carrier family 22 member 5
DGKI | diacylglycerol kinase iota
WASF1 | WAS protein family member 1
PDGFC | platelet derived growth factor C
PCYT1B | phosphate cytidylyltransferase 1, choline, beta
PRKCG | protein kinase C gamma
KRAS | KRAS proto−oncogene, GTPase
RPS6KB2 | ribosomal protein S6 kinase B2
TSC2 | TSC complex subunit 2
PIK3R2 | phosphoinositide−3−kinase regulatory subunit 2
EIF4EBP1 | eukaryotic translation initiation factor 4E binding protein 1
LYPLA1 | lysophospholipase I
RAC3 | Rac family small GTPase 3

CA SLC SS

Cancer

Color Key and Histogram

Count

Glycolysis / Gluconeogenesis
hsa00010

ADH1B | alcohol dehydrogenase 1B (class I), beta polypeptide
HKDC1 | hexokinase domain containing 1
ALDH3B1 | aldehyde dehydrogenase 3 family member B1
HK2 | hexokinase 2
ADH5 | alcohol dehydrogenase 5 (class III), chi polypeptide
G6PC3 | glucose−6−phosphatase catalytic subunit 3
BPGM | bisphosphoglycerate mutase
ADPGK | ADP dependent glucokinase
GAPDH | glyceraldehyde−3−phosphate dehydrogenase
HK3 | hexokinase 3
ENO1 | enolase 1
ALDOA | aldolase, fructose−bisphosphate A
PKM | pyruvate kinase M1/2
PGK1 | phosphoglycerate kinase 1
TPI1 | triosephosphate isomerase 1
ALDOC | aldolase, fructose−bisphosphate C
PGAM1 | phosphoglycerate mutase 1
PGM2 | phosphoglucomutase 2
ACSS1 | acyl−CoA synthetase short chain family member 1
PFKM | phosphofructokinase, muscle
ALDH7A1 | aldehyde dehydrogenase 7 family member A1
LDHAL6B | lactate dehydrogenase A like 6B
ALDH1A3 | aldehyde dehydrogenase 1 family member A3
ALDH3A2 | aldehyde dehydrogenase 3 family member A2
LDHA | lactate dehydrogenase A
LDHAL6A | lactate dehydrogenase A like 6A
PGK2 | phosphoglycerate kinase 2
GPI | glucose−6−phosphate isomerase
GAPDHS | glyceraldehyde−3−phosphate dehydrogenase, spermatogenic
PDHA1 | pyruvate dehydrogenase E1 alpha 1 subunit
ALDH9A1 | aldehyde dehydrogenase 9 family member A1
PDHB | pyruvate dehydrogenase E1 beta subunit
ADH1A | alcohol dehydrogenase 1A (class I), alpha polypeptide
ALDH3B2 | aldehyde dehydrogenase 3 family member B2
ENO3 | enolase 3

CA SLC SS

Carbohydrate metabolism

**Color Key
and Histogram**

**Pentose phosphate pathway
hsa00030**

G6PD | glucose−6−phosphate dehydrogenase

H6PD | hexose−6−phosphate dehydrogenase/glucose 1−de

PGLS | 6−phosphogluconolactonase

ALDOA | aldolase, fructose−bisphosphate A

ALDOC | aldolase, fructose−bisphosphate C

DERA | deoxyribose−phosphate aldolase

PGM2 | phosphoglucomutase 2

PFKM | phosphofructokinase, muscle

TKT | transketolase

TKTL2 | transketolase like 2

GPI | glucose−6−phosphate isomerase

TALDO1 | transaldolase 1

PGD | phosphogluconate dehydrogenase

CA   SLC   SS

Carbohydrate metabolism

Color Key and Histogram

Galactose metabolism
hsa00052

HKDC1 | hexokinase domain containing 1
GLA | galactosidase alpha
HK2 | hexokinase 2
GAA | glucosidase alpha, acid
AKR1B10 | aldo−keto reductase family 1 member B10
G6PC3 | glucose−6−phosphatase catalytic subunit 3
B4GALT2 | beta−1,4−galactosyltransferase 2
GANC | glucosidase alpha, neutral C
HK3 | hexokinase 3
GLB1 | galactosidase beta 1
B4GALT1 | beta−1,4−galactosyltransferase 1
MGAM | maltase−glucoamylase
GALT | galactose−1−phosphate uridylyltransferase
PGM2 | phosphoglucomutase 2
PFKM | phosphofructokinase, muscle
SI | sucrase−isomaltase
LCT | lactase
GALK1 | galactokinase 1
GALE | UDP−galactose−4−epimerase

CA   SLC   SS

Carbohydrate metabolism

Color Key and Histogram

Count

Ovarian steroidogenesis hsa04913

ADCY4 | adenylate cyclase 4

ADCY3 | adenylate cyclase 3

PLA2G4A | phospholipase A2 group IVA

ALOX5 | arachidonate 5−lipoxygenase

ADCY6 | adenylate cyclase 6

SCARB1 | scavenger receptor class B member 1

INSR | insulin receptor

PRKACB | protein kinase cAMP−activated catalytic subunit beta

HSD17B1 | hydroxysteroid 17−beta dehydrogenase 1

STAR | steroidogenic acute regulatory protein

CYP19A1 | cytochrome P450 family 19 subfamily A member 1

PRKACG | protein kinase cAMP−activated catalytic subunit gamm

LHB | luteinizing hormone beta polypeptide

CGA | glycoprotein hormones, alpha polypeptide

CYP11A1 | cytochrome P450 family 11 subfamily A member 1

CA   SLC   SS

Endocrine system

**Insulin signaling pathway
hsa04910**

HKDC1 | hexokinase domain containing 1
MAPK3 | mitogen-activated protein kinase 3
TRIP10 | thyroid hormone receptor interactor 10
SOCS2 | suppressor of cytokine signaling 2
PRKAR2B | protein kinase cAMP-dependent type II regulatory subunit beta
PIK3CD | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
GRB2 | growth factor receptor bound protein 2
RHOQ | ras homolog family member Q
PTPRS | protein tyrosine phosphatase receptor type S
PRKAA1 | protein kinase AMP-activated catalytic subunit alpha 1
FLOT1 | flotillin 1
INPP5K | inositol polyphosphate-5-phosphatase K
PTPN1 | protein tyrosine phosphatase, non-receptor type 1
NRAS | NRAS proto-oncogene, GTPase
PIK3CB | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta
HK2 | hexokinase 2
CBLC | Cbl proto-oncogene, adaptor protein
PIK3R5 | phosphoinositide-3-kinase regulatory subunit 5
MKNK1 | MAP kinase interacting serine/threonine kinase 1
INSR | insulin receptor
PTPRF | protein tyrosine phosphatase, receptor type F
INSR | insulin receptor
PPP1CA | protein phosphatase 1 catalytic subunit alpha
SH2B2 | SH2B adaptor protein 2
EIF4E2 | eukaryotic translation initiation factor 4E family member 2
RHEB | Ras homolog, mTORC1 binding
G6PC3 | glucose-6-phosphatase catalytic subunit 3
PDE3B | phosphodiesterase 3B
AKT1S1 | AKT1 substrate 1
PRKAR1A | protein kinase cAMP-dependent type I regulatory subunit alpha
PIK3CG | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma
HK1 | hexokinase 1
PRKAR1B | protein kinase cAMP-dependent type I regulatory subunit beta
GYS1 | glycogen synthase 1
CBLC | Cbl proto-oncogene
MAPK1 | mitogen-activated protein kinase 1
HK3 | hexokinase 3
TIAM1 | T cell lymphoma invasion and metastasis 1
BAD | BCL2 associated agonist of cell death
PIK3CA | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PRKAR2A | protein kinase cAMP-dependent type II regulatory subunit alpha
ACACB | acetyl-CoA carboxylase beta
GSK3B | glycogen synthase kinase 3 beta
PHKG1 | phosphorylase kinase catalytic subunit gamma 1
EXOC7 | exocyst complex component 7
SHC1 | SHC adaptor protein 1
PRKACB | protein kinase cAMP-activated catalytic subunit beta
MAP2K1 | mitogen-activated protein kinase kinase 2
MAP2K2 | mitogen-activated protein kinase kinase 2
PHKA2 | phosphorylase kinase regulatory subunit alpha 2
SOS1 | SOS Ras/Rac guanine nucleotide exchange factor 1
ACACA | acetyl-CoA carboxylase alpha
SLC1 | glycogen phosphorylase L
INPPL1 | inositol polyphosphate phosphatase like 1
PRKAG1 | protein kinase AMP-activated non-catalytic subunit gamma 1
PRKAB1 | protein kinase AMP-activated non-catalytic subunit beta 1
KRAS | KRAS proto-oncogene, GTPase
PRKAG2 | protein kinase AMP-activated non-catalytic subunit gamma 2
RPS6KB2 | ribosomal protein S6 kinase B2
PRKAB2 | protein kinase AMP-activated non-catalytic subunit beta 2
PRKACG | protein kinase cAMP-activated catalytic subunit gamma
BRAF | B-Raf proto-oncogene, serine/threonine kinase
IRS2 | insulin receptor substrate 2
PPP1R3D | protein phosphatase 1 regulatory subunit 3D
PPP3R2 | phosphoinositide-3-kinase regulatory subunit 2
EIF4EBP1 | eukaryotic translation initiation factor 4E binding protein 1
PHKA1 | phosphorylase kinase regulatory subunit alpha 1
GYS2 | glycogen synthase 2
CALML3 | calmodulin like 3

CA   SLC   SS

Endocrine system

**Color Key
and Histogran**

Count

−1.5 0 1

Value

GnRH signaling pathway
hsa04912

ADCY4 | adenylate cyclase 4
MMP2 | matrix metallopeptidase 2
PRKCB | protein kinase C beta
ADCY3 | adenylate cyclase 3
MAPK3 | mitogen−activated protein kinase 3
ITPR3 | inositol 1,4,5−trisphosphate receptor type 3
PLA2G4A | phospholipase A2 group IVA
GRB2 | growth factor receptor bound protein 2
CAMK2G | calcium/calmodulin dependent protein kinase II gamma
GNA11 | G protein subunit alpha 11
MAPK11 | mitogen−activated protein kinase 11
NRAS | NRAS proto−oncogene, GTPase
MMP14 | matrix metallopeptidase 14
PTK2B | protein tyrosine kinase 2 beta
ITPR1 | inositol 1,4,5−trisphosphate receptor type 1
MAP3K3 | mitogen−activated protein kinase kinase kinase 3
MAP2K6 | mitogen−activated protein kinase kinase 6
PLCB2 | phospholipase C beta 2
CDC42 | cell division cycle 42
SRC | SRC proto−oncogene, non−receptor tyrosine kinase
ADCY6 | adenylate cyclase 6
GNAQ | G protein subunit alpha q
MAP3K2 | mitogen−activated protein kinase kinase kinase 2
MAPK7 | mitogen−activated protein kinase 7
EGFR | epidermal growth factor receptor
MAPK1 | mitogen−activated protein kinase 1
PLD2 | phospholipase D2
SOS1 | SOS Ras/Rac guanine nucleotide exchange factor 1
PLD1 | phospholipase D1
PRKCD | protein kinase C delta
MAP3K1 | mitogen−activated protein kinase kinase kinase 1
MAPK14 | mitogen−activated protein kinase 14
PRKACB | protein kinase cAMP−activated catalytic subunit beta
MAP2K1 | mitogen−activated protein kinase kinase 1
MAP2K2 | mitogen−activated protein kinase kinase 2
MAPK12 | mitogen−activated protein kinase 12
PLCB4 | phospholipase C beta 4
CACNA1D | calcium voltage−gated channel subunit alpha1 D
CACNA1F | calcium voltage−gated channel subunit alpha1 F
KRAS | KRAS proto−oncogene, GTPase
MAPK13 | mitogen−activated protein kinase 13
PRKACG | protein kinase cAMP−activated catalytic subunit gamma
LHB | luteinizing hormone beta polypeptide
CGA | glycoprotein hormones, alpha polypeptide
GNRH2 | gonadotropin releasing hormone 2
CALML3 | calmodulin like 3

CA   SLC   SS

Endocrine system

**Color Key
and Histogram**

Count

0 10

−1   1

Value

Progesterone−mediated oocyte maturation
hsa04914

ADCY4 | adenylate cyclase 4
ADCY3 | adenylate cyclase 3
MAPK3 | mitogen−activated protein kinase 3
GNAI2 | G protein subunit alpha i2
CCNA2 | cyclin A2
PIK3CD | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit delta
CCNB2 | cyclin B2
RPS6KA1 | ribosomal protein S6 kinase A1
MAPK11 | mitogen−activated protein kinase 11
PIK3CB | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit beta
PIK3R5 | phosphoinositide−3−kinase regulatory subunit 5
CDK1 | cyclin dependent kinase 1
CCNB1 | cyclin B1
ADCY6 | adenylate cyclase 6
CDC27 | cell division cycle 27
BUB1 | BUB1 mitotic checkpoint serine/threonine kinase
PLK1 | polo like kinase 1
PDE3B | phosphodiesterase 3B
ARAF | A−Raf proto−oncogene, serine/threonine kinase
PIK3CG | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit gamma
CDC26 | cell division cycle 26
MAPK1 | mitogen−activated protein kinase 1
PKMYT1 | protein kinase, membrane associated tyrosine/threonine 1
CDC25C | cell division cycle 25C
FZR1 | fizzy and cell division cycle 20 related 1
CDK2 | cyclin dependent kinase 2
PIK3CA | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit alpha
GNAI1 | G protein subunit alpha i1
MAPK14 | mitogen−activated protein kinase 14
RPS6KA3 | ribosomal protein S6 kinase A3
GNAI3 | G protein subunit alpha i3
PRKACB | protein kinase cAMP−activated catalytic subunit beta
MAP2K1 | mitogen−activated protein kinase kinase 1
MAPK12 | mitogen−activated protein kinase 12
CCNA1 | cyclin A1
ANAPC5 | anaphase promoting complex subunit 5
KRAS | KRAS proto−oncogene, GTPase
CCNB3 | cyclin B3
MAPK13 | mitogen−activated protein kinase 13
PRKACG | protein kinase cAMP−activated catalytic subunit gamma
BRAF | B−Raf proto−oncogene, serine/threonine kinase
SPDYA | speedy/RINGO cell cycle regulator family member A
PIK3R2 | phosphoinositide−3−kinase regulatory subunit 2
CDC25A | cell division cycle 25A
ANAPC11 | anaphase promoting complex subunit 11
MAD2L2 | mitotic arrest deficient 2 like 2

CA   SLC   SS

Endocrine system

**Color Key
and Histogran**

Count

0 6

−1 0 1
Value

Prolactin signaling pathway
hsa04917

CCND2 | cyclin D2
MAPK3 | mitogen−activated protein kinase 3
STAT5A | signal transducer and activator of transcription 5A
SHC1 | SHC adaptor protein 1
IRF1 | interferon regulatory factor 1
SOCS2 | suppressor of cytokine signaling 2
STAT1 | signal transducer and activator of transcription 1
TNFRSF11A | TNF receptor superfamily member 11a
PIK3CD | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit delta
GRB2 | growth factor receptor bound protein 2
SOCS1 | suppressor of cytokine signaling 1
NFKB1 | nuclear factor kappa B subunit 1
STAT5B | signal transducer and activator of transcription 5B
MAPK11 | mitogen−activated protein kinase 11
NRAS | NRAS proto−oncogene, GTPase
PIK3CB | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit beta
PIK3R5 | phosphoinositide−3−kinase regulatory subunit 5
SOCS5 | suppressor of cytokine signaling 5
SRC | SRC proto−oncogene, non−receptor tyrosine kinase
JAK2 | Janus kinase 2
RELA | RELA proto−oncogene, NF−kB subunit
PIK3CG | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit gamm
MAPK1 | mitogen−activated protein kinase 1
STAT3 | signal transducer and activator of transcription 3
FOXO3 | forkhead box O3
SOS1 | SOS Ras/Rac guanine nucleotide exchange factor 1
PIK3CA | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit alpha
MAPK14 | mitogen−activated protein kinase 14
GSK3B | glycogen synthase kinase 3 beta
SHC3 | SHC adaptor protein 3
MAP2K1 | mitogen−activated protein kinase kinase 1
MAP2K2 | mitogen−activated protein kinase kinase 2
GALT | galactose−1−phosphate uridylyltransferase
MAPK12 | mitogen−activated protein kinase 12
SHC2 | SHC adaptor protein 2
TNFSF11 | TNF superfamily member 11
SOCS6 | suppressor of cytokine signaling 6
SHC4 | SHC adaptor protein 4
KRAS | KRAS proto−oncogene, GTPase
MAPK13 | mitogen−activated protein kinase 13
LHB | luteinizing hormone beta polypeptide
CGA | glycoprotein hormones, alpha polypeptide
PIK3R2 | phosphoinositide−3−kinase regulatory subunit 2
TH | tyrosine hydroxylase
PRLR | prolactin receptor

CA

SLC

SS

Endocrine system

Color Key and Histogran

Count

0 30

−3 0 2

Value

Leukocyte transendothelial migration
hsa04670

PECAM1 | platelet and endothelial cell adhesion molecule 1
MYL9 | myosin light chain 9
RAC2 | Rac family small GTPase 2
CLDN5 | claudin 5
ESAM | endothelial cell adhesion molecule
MSN | moesin
CLDN4 | claudin 7
THY1 | Thy-1 cell surface antigen
ICAM1 | intercellular adhesion molecule 1
MMP9 | matrix metallopeptidase 9
ACTN1 | actinin alpha 1
MMP2 | matrix metallopeptidase 2
CYBA | cytochrome b-245 alpha chain
PRKCB | protein kinase C beta
VASP | vasodilator stimulated phosphoprotein
VCL | vinculin
PXN | paxillin
CYBB | cytochrome b-245 beta chain
GNAI2 | G protein subunit alpha i2
CTNNB1 | catenin beta 1
VCAM1 | vascular cell adhesion molecule 1
ROCK2 | Rho associated coiled-coil containing protein kinase 2
NCF4 | neutrophil cytosolic factor 4
PIK3CD | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
NCF2 | neutrophil cytosolic factor 2
MYL12B | myosin light chain 12B
ACTN4 | actinin alpha 4
RAP1A | RAP1A, member of RAS oncogene family
PLCG2 | phospholipase C gamma 2
ITGAM | integrin subunit alpha M
F11R | F11 receptor
CLDN15 | claudin 15
SIPA1 | signal-induced proliferation-associated 1
ACTB | actin beta
MAPK11 | mitogen-activated protein kinase 11
ROCK1 | Rho associated coiled-coil containing protein kinase 1
ARHGEF5 | Rho guanine nucleotide exchange factor 3
PTK2B | protein tyrosine kinase 2 beta
PIK3CB | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta
VAV2 | vav guanine nucleotide exchange factor 1
MYL12A | myosin light chain 12A
PIK3R5 | phosphoinositide-3-kinase regulatory subunit 5
BCAR1 | BCAR1, Cas family scaffolding protein
RASSF5 | Ras association domain family member 5
CDC42 | cell division cycle 42
RHOA | ras homolog family member A
RAC1 | Rac family small GTPase 1
PIK3CG | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma
PIK3CA | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
GNAI3 | G protein subunit alpha i1
MAPK14 | mitogen-activated protein kinase 14
CLDN3 | claudin 3
CTNNA1 | catenin alpha 1
GNAI3 | G protein subunit alpha i3
CLDN19 | claudin 19
MAPK12 | mitogen-activated protein kinase 12
CLDN6 | claudin 6
PECAM1 | gamma 1
PRKCG | protein kinase C gamma
MYL7 | myosin light chain 7
ACTN3 | actinin alpha 3 (gene/pseudogene)
MYL10 | myosin light chain 10
NOX3 | NADPH oxidase 3
MAPK13 | mitogen-activated protein kinase 13
CLDN11 | claudin 11
CLDN14 | claudin 14
PIK3R2 | phosphoinositide-3-kinase regulatory subunit 2
CLDN9 | claudin 9

CA   SLC   SS

Immune system

Color Key
and Histogran

Count

−2   0   2

Value

Platelet activation
hsa04611

COL1A2 | collagen type I alpha 2 chain
VWF | von Willebrand factor
COL1A1 | collagen type I alpha 1 chain
APBB1IP | amyloid beta precursor protein binding family B member 1 interacting protein
TLN1 | talin 1
VASP | vasodilator stimulated phosphoprotein
ADCY3 | adenylate cyclase 3
MAPK3 | mitogen-activated protein kinase 3
GNA12 | G protein subunit alpha 12
COL24A1 | collagen type XXIV alpha 1 chain
FERMT3 | fermitin family member 3
GNA13 | G protein subunit alpha 13
PRKG1 | protein kinase, cGMP-dependent, type I
FCER1G | Fc fragment of IgE receptor Ig
GUCY1B3 | guanylate cyclase 1 soluble subunit beta
P2RY12 | purinergic receptor P2Y12
ROCK2 | Rho associated coiled-coil containing protein kinase 2
P2RX1 | purinergic receptor P2X 1
PLA2G4A | phospholipase A2 group IVA
PIK3CD | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
MRAS | muscle RAS oncogene homolog
MYL12B | myosin light chain 12B
PLCG2 | phospholipase C gamma 2
COL4A3 | collagen type IV alpha 3 chain
RASGRP2 | RAS guanyl releasing protein 2
RASGRP1 | RAS guanyl releasing protein 1
COL5A1 | collagen type V alpha 1 chain
COL5A4 | collagen type V alpha 4 chain
F2RL3 | F2R like thrombin or trypsin receptor 3
ACTB | actin beta
F2R | coagulation factor II thrombin receptor
MAPK11 | mitogen-activated protein kinase 11
SYK | spleen associated tyrosine kinase
ROCK1 | Rho associated coiled-coil containing protein kinase 1
PPP1R12A | protein phosphatase 1 regulatory subunit 12A
BTK | Bruton tyrosine kinase
PIK3CB | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta
ITPR1 | inositol 1,4,5-trisphosphate receptor type 1
MYL12A | myosin light chain 12A
SNAP23 | synaptosome associated protein 23
PIK3R5 | phosphoinositide-3-kinase regulatory subunit 5
LYN | LYN proto-oncogene, Src family tyrosine kinase
ITGB3 | integrin subunit beta 3
PLCB2 | phospholipase C beta 2
SRC | SRC proto-oncogene, non-receptor tyrosine kinase
ADCY6 | adenylate cyclase 6
GNAO1 | G protein subunit alpha o
PIK3CA | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
RHOA | ras homolog family member A
PIK3CG | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma
PRKG2 | protein kinase, cGMP-dependent, type II
P2RY1 | purinergic receptor P2Y1
MAPK1 | mitogen-activated protein kinase 1
ADCY2 | adenylate cyclase 2
ARHGEF12 | Rho guanine nucleotide exchange factor 12
PIK3CA | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
GNAI1 | G protein subunit alpha i1
MAPK14 | mitogen-activated protein kinase 14
GNAI3 | G protein subunit alpha i3
PRKACB | protein kinase cAMP-activated catalytic subunit beta
PRKACB | protein kinase cAMP-activated catalytic subunit beta
MAPK12 | mitogen-activated protein kinase 12
MYLK4 | myosin light chain kinase family member 4
TBXAS1 | stromal interaction molecule 1
TBXAS1 | thromboxane A synthase 1
ITGA2 | integrin subunit alpha 2
COL24A1 | collagen type XXIV alpha 1 chain
PLCB4 | phospholipase C beta 4
ACTG1 | actin gamma 1
MAPK13 | mitogen-activated protein kinase 13
PRKACG | protein kinase cAMP-activated catalytic subunit gamma
MYLK2 | myosin light chain kinase 2
PIK3R2 | phosphoinositide-3-kinase regulatory subunit 2
COL2A1 | collagen type II alpha 1 chain
FGB | fibrinogen beta chain

CA   SLC   SS

Immune system

Antigen processing and presentation
hsa04612

HLA−B | major histocompatibility complex, class I, B
HLA−F | major histocompatibility complex, class I, F
HLA−E | major histocompatibility complex, class I, E
TAP1 | transporter 1, ATP binding cassette subfamily B member
HLA−C | major histocompatibility complex, class I, C
TAP2 | transporter 2, ATP binding cassette subfamily B member
B2M | beta−2−microglobulin
TAPBP | TAP binding protein
CTSL | cathepsin L
HLA−G | major histocompatibility complex, class I, G
PSME3 | proteasome activator subunit 3
CANX | calnexin
RFXANK | regulatory factor X associated ankyrin containing protein
CALR | calreticulin
TNF | tumor necrosis factor
HSPA1L | heat shock protein family A (Hsp70) member 1 like
HSPA5 | heat shock protein family A (Hsp70) member 5
IFI30 | IFI30, lysosomal thiol reductase
NFYC | nuclear transcription factor Y subunit gamma
KIR2DL4 | killer cell immunoglobulin like receptor, two Ig domains and lo
CTSB | cathepsin B
HSPA6 | heat shock protein family A (Hsp70) member 6

CA
SLC
SS

Immune system

**Color Key
and Histogran**

Count

**Toll−like receptor signaling pathway
hsa04620**

CXCL9 | C−X−C motif chemokine ligand 9
CTSK | cathepsin K
NFKBIA | NFKB inhibitor alpha
MAP3K8 | mitogen−activated protein kinase kinase kinase 8
MAPK3 | mitogen−activated protein kinase 3
LY96 | lymphocyte antigen 96
STAT1 | signal transducer and activator of transcription 1
PIK3CD | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit delta
CD14 | CD14 molecule
SPP1 | secreted phosphoprotein 1
NFKB1 | nuclear factor kappa B subunit 1
TLR3 | toll like receptor 3
IRF7 | interferon regulatory factor 7
MAPK11 | mitogen−activated protein kinase 11
RIPK1 | receptor interacting serine/threonine kinase 1
PIK3CB | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit beta
PIK3R5 | phosphoinositide−3−kinase regulatory subunit 5
IL1B | interleukin 1 beta
IFNAR2 | interferon alpha and beta receptor subunit 2
MAP2K6 | mitogen−activated protein kinase kinase 6
TICAM1 | toll like receptor adaptor molecule 1
CASP8 | caspase 8
RELA | RELA proto−oncogene, NF−kB subunit
CHUK | conserved helix−loop−helix ubiquitous kinase
IRF3 | interferon regulatory factor 3
RAC1 | Rac family small GTPase 1
TLR1 | toll like receptor 1
PIK3CG | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit gamma
IKBKG | inhibitor of nuclear factor kappa B kinase subunit gamma
TLR2 | toll like receptor 2
MAPK1 | mitogen−activated protein kinase 1
FADD | Fas associated via death domain
IFNAR1 | interferon alpha and beta receptor subunit 1
CD80 | CD80 molecule
PIK3CA | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit alpha
MAPK14 | mitogen−activated protein kinase 14
TLR6 | toll like receptor 6
TNF | tumor necrosis factor
TLR8 | toll like receptor 8
MAP2K1 | mitogen−activated protein kinase kinase 1
MAP2K2 | mitogen−activated protein kinase kinase 2
MAPK12 | mitogen−activated protein kinase 12
TBK1 | TANK binding kinase 1
TIRAP | TIR domain containing adaptor protein
IL12A | interleukin 12A
IL12B | interleukin 12B
MYD88 | myeloid differentiation primary response 88
IRAK4 | interleukin 1 receptor associated kinase 4
TLR9 | toll like receptor 9
IKBKE | inhibitor of nuclear factor kappa B kinase subunit epsilon
IFNA5 | interferon alpha 5
IFNA21 | interferon alpha 21
MAPK13 | mitogen−activated protein kinase 13
IFNB1 | interferon beta 1
LBP | lipopolysaccharide binding protein
PIK3R2 | phosphoinositide−3−kinase regulatory subunit 2

CA

SLC

SS

Immune system

**Color Key
and Histogran**

Count

RIG−I−like receptor signaling pathway
hsa04622

TMEM173 | transmembrane protein 173
NFKBIA | NFKB inhibitor alpha
CASP10 | caspase 10
ISG15 | ISG15 ubiquitin−like modifier
TRIM25 | tripartite motif containing 25
NFKB1 | nuclear factor kappa B subunit 1
IRF7 | interferon regulatory factor 7
MAPK11 | mitogen−activated protein kinase 11
RIPK1 | receptor interacting serine/threonine kinase 1
NFKBIB | NFKB inhibitor beta
TANK | TRAF family member associated NFKB activator
CASP8 | caspase 8
RELA | RELA proto−oncogene, NF−kB subunit
RNF125 | ring finger protein 125
CHUK | conserved helix−loop−helix ubiquitous kinase
ATG12 | autophagy related 12
IRF3 | interferon regulatory factor 3
PIN1 | peptidylprolyl cis/trans isomerase, NIMA−interacting 1
IKBKG | inhibitor of nuclear factor kappa B kinase subunit gamma
FADD | Fas associated via death domain
DDX3X | DEAD−box helicase 3, X−linked
OTUD5 | OTU deubiquitinase 5
SIKE1 | suppressor of IKBKE 1
MAP3K1 | mitogen−activated protein kinase kinase kinase 1
MAPK14 | mitogen−activated protein kinase 14
TNF | tumor necrosis factor
MAVS | mitochondrial antiviral signaling protein
MAPK12 | mitogen−activated protein kinase 12
TBK1 | TANK binding kinase 1
IL12A | interleukin 12A
IFNE | interferon epsilon
IL12B | interleukin 12B
IKBKE | inhibitor of nuclear factor kappa B kinase subunit epsilon
IFNA5 | interferon alpha 5
IFNA21 | interferon alpha 21
IFNW1 | interferon omega 1
MAPK13 | mitogen−activated protein kinase 13
IFNB1 | interferon beta 1
IFNK | interferon kappa

CA   SLC   SS

Immune system

**Color Key
and Histogram**

Count

−1.5   0   1
Value

Fc epsilon RI signaling pathway
hsa04664

RAC2 | Rac family small GTPase 2
PRKCB | protein kinase C beta
MAPK3 | mitogen−activated protein kinase 3
FCER1G | Fc fragment of IgE receptor Ig
INPP5D | inositol polyphosphate−5−phosphatase D
PLA2G4A | phospholipase A2 group IVA
PIK3CD | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit delta
GRB2 | growth factor receptor bound protein 2
FCER1A | Fc fragment of IgE receptor Ia
PLCG2 | phospholipase C gamma 2
GAB2 | GRB2 associated binding protein 2
LCP2 | lymphocyte cytosolic protein 2
MS4A2 | membrane spanning 4−domains A2
MAPK11 | mitogen−activated protein kinase 11
SYK | spleen associated tyrosine kinase
NRAS | NRAS proto−oncogene, GTPase
BTK | Bruton tyrosine kinase
PIK3CB | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit beta
VAV1 | vav guanine nucleotide exchange factor 1
PIK3R5 | phosphoinositide−3−kinase regulatory subunit 5
LYN | LYN proto−oncogene, Src family tyrosine kinase
MAP2K6 | mitogen−activated protein kinase kinase 6
RAC1 | Rac family small GTPase 1
PIK3CG | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit gamma
MAPK1 | mitogen−activated protein kinase 1
SOS1 | SOS Ras/Rac guanine nucleotide exchange factor 1
PRKCD | protein kinase C delta
PIK3CA | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit alpha
MAPK14 | mitogen−activated protein kinase 14
TNF | tumor necrosis factor
PDPK1 | 3−phosphoinositide dependent protein kinase 1
MAP2K1 | mitogen−activated protein kinase kinase 1
MAP2K2 | mitogen−activated protein kinase kinase 2
MAPK12 | mitogen−activated protein kinase 12
KRAS | KRAS proto−oncogene, GTPase
IL3 | interleukin 3
IL5 | interleukin 5
MAPK13 | mitogen−activated protein kinase 13
PIK3R2 | phosphoinositide−3−kinase regulatory subunit 2
RAC3 | Rac family small GTPase 3

CA   SLC   SS

Immune system

Color Key and Histogram

Count

0 15

−1.5   0   1

Value

Fc gamma R−mediated phagocytosis
hsa04666

RAC2 | Rac family small GTPase 2
GSN | gelsolin
ARPC1B | actin related protein 2/3 complex subunit 1B
PRKCB | protein kinase C beta
VASP | vasodilator stimulated phosphoprotein
PTPRC | protein tyrosine phosphatase, receptor type C
ARPC5 | actin related protein 2/3 complex subunit 5
MAPK3 | mitogen−activated protein kinase 3
PIP5K1B | phosphatidylinositol−4−phosphate 5−kinase type 1 beta
INPP5D | inositol polyphosphate−5−phosphatase D
PLA2G4A | phospholipase A2 group IVA
PIK3CD | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit delta
CFL2 | cofilin 2
HCK | HCK proto−oncogene, Src family tyrosine kinase
ASAP1 | ArfGAP with SH3 domain, ankyrin repeat and PH domain 1
MARCKS | myristoylated alanine rich protein kinase C substrate
PLCG2 | phospholipase C gamma 2
GAB2 | GRB2 associated binding protein 2
WASF1 | p21 (RAC1) activated kinase 1
ARPC1A | actin related protein 2/3 complex subunit 1A
CFL1 | cofilin 1
ARPC4 | actin related protein 2/3 complex subunit 4
LIMK2 | LIM domain kinase 2
SYK | spleen associated tyrosine kinase
WASF2 | WAS protein family member 2
WAS | Wiskott−Aldrich syndrome
PIK3CB | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit beta
VAV1 | vav guanine nucleotide exchange factor 1
PIK3R5 | phosphoinositide−3−kinase regulatory subunit 5
LYN | LYN proto−oncogene, Src family tyrosine kinase
CRK | CRK proto−oncogene, adaptor protein
CDC42 | cell division cycle 42
ARPC3 | actin related protein 2/3 complex subunit 3
DNM2 | dynamin 2
DOCK2 | dedicator of cytokinesis 2
RAC1 | Rac family small GTPase 1
PIK3CG | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit gamma
MAPK1 | mitogen−activated protein kinase 1
ARPC2 | actin related protein 2/3 complex subunit 2
LIMK1 | LIM domain kinase 1
PLD2 | phospholipase D2
PLD1 | phospholipase D1
FCGR1A | Fc fragment of IgG receptor Ia
PIP5K1A | phosphatidylinositol−4−phosphate 5−kinase type 1 alpha
PRKCD | protein kinase C delta
PIK3CA | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit alpha
SPHK2 | sphingosine kinase 2
MAP2K1 | mitogen−activated protein kinase kinase 1
WASL | Wiskott−Aldrich syndrome like
WASF1 | WAS protein family member 1
INPPL1 | inositol polyphosphate phosphatase like 1
PRKCG | protein kinase C gamma
FCGR2B | Fc fragment of IgG receptor IIb
RPS6KB2 | ribosomal protein S6 kinase B2
MYO10 | myosin X
ARF6 | ADP ribosylation factor 6
PIK3R2 | phosphoinositide−3−kinase regulatory subunit 2
SPHK1 | sphingosine kinase 1
SCIN | scinderin

CA   SLC   SS

Immune system

**Color Key
and Histogram**

Count

−1 0 1
Value

Bacterial invasion of epithelial cells
hsa05100

ITGA5 | integrin subunit alpha 5
CAV2 | caveolin 2
ARPC1B | actin related protein 2/3 complex subunit 1B
VCL | vinculin
PXN | paxillin
ARPC5 | actin related protein 2/3 complex subunit 5
RHOG | ras homolog family member G
SHC1 | SHC adaptor protein 1
ILK | integrin linked kinase
FN1 | fibronectin 1
PIK3CD | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit delta
CTNNB1 | catenin beta 1
DOCK1 | dedicator of cytokinesis 1
ARPC1A | actin related protein 2/3 complex subunit 1A
ACTB | actin beta
ARPC4 | actin related protein 2/3 complex subunit 4
WASF2 | WAS protein family member 2
WAS | Wiskott−Aldrich syndrome
PIK3CB | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit beta
HCLS1 | hematopoietic cell−specific Lyn substrate 1
PIK3R5 | phosphoinositide−3−kinase regulatory subunit 5
BCAR1 | BCAR1, Cas family scaffolding protein
CRK | CRK proto−oncogene, adaptor protein
MET | MET proto−oncogene, receptor tyrosine kinase
SEPT2 | septin 2
GAB1 | GRB2 associated binding protein 1
CDC42 | cell division cycle 42
SRC | SRC proto−oncogene, non−receptor tyrosine kinase
ARPC3 | actin related protein 2/3 complex subunit 3
DNM2 | dynamin 2
RHOA | ras homolog family member A
RAC1 | Rac family small GTPase 1
PIK3CG | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit gamma
DNM1 | dynamin 1
CBL | Cbl proto−oncogene
CLTB | clathrin light chain B
CLTC | clathrin heavy chain
ARPC2 | actin related protein 2/3 complex subunit 2
PIK3CA | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit alpha
CTNNA1 | catenin alpha 1
SHC3 | SHC adaptor protein 3
ELMO2 | engulfment and cell motility 2
WASL | Wiskott−Aldrich syndrome like
ARHGAP10 | Rho GTPase activating protein 10
SHC2 | SHC adaptor protein 2
DNM3 | dynamin 3
CLTA | clathrin light chain A
WASF1 | WAS protein family member 1
SHC4 | SHC adaptor protein 4
ACTG1 | actin gamma 1
SEPT8 | septin 8
CAV3 | caveolin 3
SEPT12 | septin 12
CLTCL1 | clathrin heavy chain like 1
PIK3R2 | phosphoinositide−3−kinase regulatory subunit 2
ELMO3 | engulfment and cell motility 3
MAD2L2 | mitotic arrest deficient 2 like 2
SEPT3 | septin 3

CA   SLC   SS

Infectious disease

**Color Key
and Histogran**

Count

−1　0　1
Value

Vibrio cholerae infection
hsa05110

PRKCB | protein kinase C beta
ADCY3 | adenylate cyclase 3
KCNQ1 | potassium voltage−gated channel subfamily Q member 1
PLCG2 | phospholipase C gamma 2
ACTB | actin beta
TCIRG1 | T−cell immune regulator 1, ATPase H+ transporting V0 subunit a3
ATP6V1C1 | ATPase H+ transporting V1 subunit C1
SEC61G | Sec61 translocon gamma subunit
ATP6V1E1 | ATPase H+ transporting V1 subunit E1
KDELR1 | KDEL endoplasmic reticulum protein retention receptor 1
CFTR | cystic fibrosis transmembrane conductance regulator
ATP6V0A1 | ATPase H+ transporting V0 subunit a1
ATP6V0B | ATPase H+ transporting V0 subunit b
ATP6V0E1 | ATPase H+ transporting V0 subunit e1
TJP2 | tight junction protein 2
ATP6V1B2 | ATPase H+ transporting V1 subunit B2
ATP6V0D1 | ATPase H+ transporting V0 subunit d1
ATP6AP1 | ATPase H+ transporting accessory protein 1
ATP6V0C | ATPase H+ transporting V0 subunit c
ARF1 | ADP ribosylation factor 1
KDELR3 | KDEL endoplasmic reticulum protein retention receptor 3
PRKACB | protein kinase cAMP−activated catalytic subunit beta
KDELR2 | KDEL endoplasmic reticulum protein retention receptor 2
SEC61A1 | Sec61 translocon alpha 1 subunit
ATP6V1A | ATPase H+ transporting V1 subunit A
ATP6V1H | ATPase H+ transporting V1 subunit H
ACTG1 | actin gamma 1
PRKCG | protein kinase C gamma
ATP6V1B1 | ATPase H+ transporting V1 subunit B1
PRKACG | protein kinase cAMP−activated catalytic subunit gamma
ATP6V1F | ATPase H+ transporting V1 subunit F
SEC61A2 | Sec61 translocon alpha 2 subunit
ERO1A | endoplasmic reticulum oxidoreductase 1 alpha
ATP6V1C2 | ATPase H+ transporting V1 subunit C2
ATP6V0E2 | ATPase H+ transporting V0 subunit e2

CA　SLC　SS

Infectious disease

**Color Key
and Histogram**

Epithelial cell signaling in Helicobacter pylori infection hsa05120

Count

−1 0 1
Value

CXCL1 | C−X−C motif chemokine ligand 1
NFKBIA | NFKB inhibitor alpha
ADAM10 | ADAM metallopeptidase domain 10
PLCG2 | phospholipase C gamma 2
F11R | F11 receptor
PAK1 | p21 (RAC1) activated kinase 1
NFKB1 | nuclear factor kappa B subunit 1
MAPK11 | mitogen−activated protein kinase 11
TCIRG1 | T−cell immune regulator 1, ATPase H+ transporting V0 subunit a3
ATP6V1C1 | ATPase H+ transporting V1 subunit C1
LYN | LYN proto−oncogene, Src family tyrosine kinase
MET | MET proto−oncogene, receptor tyrosine kinase
ATP6V1E1 | ATPase H+ transporting V1 subunit E1
CDC42 | cell division cycle 42
SRC | SRC proto−oncogene, non−receptor tyrosine kinase
RELA | RELA proto−oncogene, NF−kB subunit
CHUK | conserved helix−loop−helix ubiquitous kinase
RAC1 | Rac family small GTPase 1
EGFR | epidermal growth factor receptor
ATP6V0A1 | ATPase H+ transporting V0 subunit a1
ATP6V0B | ATPase H+ transporting V0 subunit b
IKBKG | inhibitor of nuclear factor kappa B kinase subunit gamma
ATP6V0E1 | ATPase H+ transporting V0 subunit e1
ATP6V1B2 | ATPase H+ transporting V1 subunit B2
ADAM17 | ADAM metallopeptidase domain 17
CSK | C−terminal Src kinase
ATP6V0D1 | ATPase H+ transporting V0 subunit d1
CXCR1 | C−X−C motif chemokine receptor 1
MAPK14 | mitogen−activated protein kinase 14
ATP6AP1 | ATPase H+ transporting accessory protein 1
ATP6V0C | ATPase H+ transporting V0 subunit c
MAPK12 | mitogen−activated protein kinase 12
ATP6V1A | ATPase H+ transporting V1 subunit A
ATP6V1H | ATPase H+ transporting V1 subunit H
ATP6V1B1 | ATPase H+ transporting V1 subunit B1
MAPK13 | mitogen−activated protein kinase 13
ATP6V1F | ATPase H+ transporting V1 subunit F
ATP6V1C2 | ATPase H+ transporting V1 subunit C2
ATP6V0E2 | ATPase H+ transporting V0 subunit e2

CA SLC SS

Infectious disease

**Color Key
and Histogran**

Count

−1.5 0 1

Value

Salmonella infection
hsa05132

FLNA | filamin A
PYCARD | PYD and CARD domain containing
CXCL1 | C−X−C motif chemokine ligand 1
IFNGR1 | interferon gamma receptor 1
ARPC1B | actin related protein 2/3 complex subunit 1B
MYH14 | myosin heavy chain 14
CASP1 | caspase 1
ARPC5 | actin related protein 2/3 complex subunit 5
PKN3 | protein kinase N3
MAPK3 | mitogen−activated protein kinase 3
RHOG | ras homolog family member G
MYH9 | myosin heavy chain 9
ROCK2 | Rho associated coiled−coil containing protein kinase 2
CD14 | CD14 molecule
IL18 | interleukin 18
ARPC1A | actin related protein 2/3 complex subunit 1A
PFN1 | profilin 1
PKN2 | protein kinase N2
NFKB1 | nuclear factor kappa B subunit 1
ACTB | actin beta
CXCL3 | C−X−C motif chemokine ligand 3
RAB7B | RAB7B, member RAS oncogene family
ARPC4 | actin related protein 2/3 complex subunit 4
MAPK11 | mitogen−activated protein kinase 11
FLNB | filamin B
ROCK1 | Rho associated coiled−coil containing protein kinase 1
WASF2 | WAS protein family member 2
WAS | Wiskott−Aldrich syndrome
DYNC1LI2 | dynein cytoplasmic 1 light intermediate chain 2
RAB7A | RAB7A, member RAS oncogene family
IL1B | interleukin 1 beta
PKN1 | protein kinase N1
IFNGR2 | interferon gamma receptor 2
CDC42 | cell division cycle 42
ARPC3 | actin related protein 2/3 complex subunit 3
DYNC1H1 | dynein cytoplasmic 1 heavy chain 1
RELA | RELA proto−oncogene, NF−kB subunit
NOS2 | nitric oxide synthase 2
RAC1 | Rac family small GTPase 1
DYNC2H1 | dynein cytoplasmic 2 heavy chain 1
PLEKHM2 | pleckstrin homology and RUN domain containing M2
MAPK1 | mitogen−activated protein kinase 1
ARPC2 | actin related protein 2/3 complex subunit 2
RILP | Rab interacting lysosomal protein
MAPK14 | mitogen−activated protein kinase 14
KLC1 | kinesin light chain 1
NLRC4 | NLR family CARD domain containing 4
MAPK12 | mitogen−activated protein kinase 12
WASL | Wiskott−Aldrich syndrome like
WASF1 | WAS protein family member 1
ACTG1 | actin gamma 1
DYNC1LI1 | dynein cytoplasmic 1 light intermediate chain 1
MYD88 | myeloid differentiation primary response 88
IL1A | interleukin 1 alpha
MAPK13 | mitogen−activated protein kinase 13
LBP | lipopolysaccharide binding protein
PFN4 | profilin family member 4

CA

SLC

SS

Infectious disease

**Color Key
and Histogran**

Count

0   6

−1   0   1

Value

**Pertussis
hsa05133**

ITGA5 | integrin subunit alpha 5
PYCARD | PYD and CARD domain containing
SERPING1 | serpin family G member 1
C1S | complement C1s
CASP1 | caspase 1
C1QA | complement C1q A chain
MAPK3 | mitogen−activated protein kinase 3
C3 | complement C3
GNAI2 | G protein subunit alpha i2
C1R | complement C1r
ITGB2 | integrin subunit beta 2
IRF1 | interferon regulatory factor 1
LY96 | lymphocyte antigen 96
C2 | complement C2
C1QB | complement C1q B chain
CFL2 | cofilin 2
CXCL6 | C−X−C motif chemokine ligand 6
CD14 | CD14 molecule
ITGAM | integrin subunit alpha M
C1QC | complement C1q C chain
NFKB1 | nuclear factor kappa B subunit 1
CFL1 | cofilin 1
MAPK11 | mitogen−activated protein kinase 11
IL1B | interleukin 1 beta
TICAM1 | toll like receptor adaptor molecule 1
RELA | RELA proto−oncogene, NF−kB subunit
NLRP3 | NLR family pyrin domain containing 3
NOS2 | nitric oxide synthase 2
RHOA | ras homolog family member A
IRF3 | interferon regulatory factor 3
MAPK1 | mitogen−activated protein kinase 1
GNAI1 | G protein subunit alpha i1
MAPK14 | mitogen−activated protein kinase 14
TNF | tumor necrosis factor
GNAI3 | G protein subunit alpha i3
MAPK12 | mitogen−activated protein kinase 12
TIRAP | TIR domain containing adaptor protein
IL12A | interleukin 12A
C4BPA | complement component 4 binding protein alpha
IL12B | interleukin 12B
MYD88 | myeloid differentiation primary response 88
IL1A | interleukin 1 alpha
IRAK4 | interleukin 1 receptor associated kinase 4
MAPK13 | mitogen−activated protein kinase 13
C4BPB | complement component 4 binding protein beta
CALML3 | calmodulin like 3

CA   SLC   SS

Infectious disease

**Color Key
and Histogram**

Count

**Legionellosis
hsa05134**

Value

PYCARD | PYD and CARD domain containing
CXCL1 | C−X−C motif chemokine ligand 1
NFKBIA | NFKB inhibitor alpha
CASP1 | caspase 1
C3 | complement C3
NFKB2 | nuclear factor kappa B subunit 2
ITGB2 | integrin subunit beta 2
CD14 | CD14 molecule
IL18 | interleukin 18
ITGAM | integrin subunit alpha M
NFKB1 | nuclear factor kappa B subunit 1
CXCL3 | C−X−C motif chemokine ligand 3
IL1B | interleukin 1 beta
APAF1 | apoptotic peptidase activating factor 1
CASP8 | caspase 8
RAB1A | RAB1A, member RAS oncogene family
RELA | RELA proto−oncogene, NF−kB subunit
HSF1 | heat shock transcription factor 1
SAR1A | secretion associated Ras related GTPase 1A
TLR2 | toll like receptor 2
RAB1B | RAB1B, member RAS oncogene family
TNF | tumor necrosis factor
HSPA1L | heat shock protein family A (Hsp70) member 1 like
VCP | valosin containing protein
ARF1 | ADP ribosylation factor 1
NLRC4 | NLR family CARD domain containing 4
SEC22B | SEC22 homolog B, vesicle trafficking protein (gene/pseudogene)
BCL2L13 | BCL2 like 13
IL12A | interleukin 12A
IL12B | interleukin 12B
NAIP | NLR family apoptosis inhibitory protein
MYD88 | myeloid differentiation primary response 88
HBS1L | HBS1 like translational GTPase
HSPA6 | heat shock protein family A (Hsp70) member 6
BNIP3 | BCL2 interacting protein 3
EEF1A2 | eukaryotic translation elongation factor 1 alpha 2

CA

SLC

SS

Infectious disease

Color Key and Histogram

Count

Chagas disease (American trypanosomiasis) hsa05142

SERPINE1 | serpin family E member 1
TGFB1 | transforming growth factor beta 1
TGFBR2 | transforming growth factor beta receptor 2
IFNGR1 | interferon gamma receptor 1
NFKBIA | NFKB inhibitor alpha
ACE | angiotensin I converting enzyme
C1QA | complement C1q A chain
MAPK3 | mitogen-activated protein kinase 3
C3 | complement C3
GNAI2 | G protein subunit alpha i2
C1QB | complement C1q B chain
PIK3CD | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
TGFB2 | transforming growth factor beta 2
C1QC1 | complement C1q C chain
GNA11 | G protein subunit alpha 11
NFKB1 | nuclear factor kappa B subunit 1
MAPK11 | mitogen-activated protein kinase 11
TNFRSF1A | TNF receptor superfamily member 1A
FAS | Fas cell surface death receptor
CFLAR | CASP8 and FADD like apoptosis regulator
PIK3CB | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta
PIK3R5 | phosphoinositide-3-kinase regulatory subunit 5
PPP2CB | protein phosphatase 2 catalytic subunit beta
TGFB3 | transforming growth factor beta 3
IL1B | interleukin 1 beta
IFNGR2 | interferon gamma receptor 2
PLCB2 | phospholipase C beta 2
TICAM1 | toll like receptor adaptor molecule 1
CASP8 | caspase 8
GNAQ | G protein subunit alpha q
TGFBR1 | transforming growth factor beta receptor 1
RELA | RELA proto-oncogene, NF-kB subunit
NOS2 | nitric oxide synthase 2
CHUK | conserved helix-loop-helix ubiquitous kinase
PIK3CG | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma
IKBKG | inhibitor of nuclear factor kappa B kinase subunit gamma
TLR2 | toll like receptor 2
MAPK1 | mitogen-activated protein kinase 1
FADD | Fas associated via death domain
PPP2CA | protein phosphatase 2 catalytic subunit alpha
PIK3CA | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
GNAI1 | G protein subunit alpha i1
MAPK14 | mitogen-activated protein kinase 14
TLR6 | toll like receptor 6
CALR | calreticulin
TNF | tumor necrosis factor
GNAI3 | G protein subunit alpha i3
MAPK12 | mitogen-activated protein kinase 12
PPP2R2A | protein phosphatase 2 regulatory subunit Balpha
IL12A | interleukin 12A
PLCB4 | phospholipase C beta 4
IL12B | interleukin 12B
MYD88 | myeloid differentiation primary response 88
IRAK4 | interleukin 1 receptor associated kinase 4
TLR9 | toll like receptor 9
MAPK13 | mitogen-activated protein kinase 13
IFNB1 | interferon beta 1
PIK3R2 | phosphoinositide-3-kinase regulatory subunit 2
GNA15 | G protein subunit alpha 15
PPP2R2C | protein phosphatase 2 regulatory subunit Bgamma

CA   SLC   SS

Infectious disease

**Color Key
and Histogran**

Count

**Amoebiasis
hsa05146**

−3　0　2

Value

COL4A2 | collagen type IV alpha 2 chain
LAMA3 | laminin subunit alpha 3
COL4A1 | collagen type IV alpha 1 chain
LAMC2 | laminin subunit gamma 2
COL4A2 | collagen type IV alpha 2 chain
TGFB1 | transforming growth factor beta 1
COL1A1 | collagen type I alpha 1 chain
LAMB3 | laminin subunit beta 3
COL3A1 | collagen type III alpha 1 chain
CXCL1 | C−X−C motif chemokine ligand 1
LAMC1 | laminin subunit gamma 1
ACTN1 | actinin alpha 1
PRKCB | protein kinase C beta
VCL | vinculin
LAMB1 | laminin subunit beta 1
ITGB2 | integrin subunit beta 2
COL27A1 | collagen type XXVII alpha 1 chain
FN1 | fibronectin 1
RAB5C | RAB5C, member RAS oncogene family
PIK3CD | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit delta
LAMC3 | laminin subunit gamma 3
SERPINB6 | serpin family B member 6
ACTN4 | actinin alpha 4
CD14 | CD14 molecule
TGFB2 | transforming growth factor beta 2
COL5A3 | collagen type V alpha 3 chain
ITGAM | integrin subunit alpha M
COL5A2 | collagen type V alpha 2 chain
COL5A1 | collagen type V alpha 1 chain
SERPINB1 | serpin family B member 1
GNAI1 | G protein subunit alpha I1
NFKB1 | nuclear factor kappa B subunit 1
RAB7B | RAB7B, member RAS oncogene family
PIK3CB | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit beta
PIK3R5 | phosphoinositide−3−kinase regulatory subunit 5
RAB7A | RAB7A, member RAS oncogene family
TGFB3 | transforming growth factor beta 3
IL1B | interleukin 1 beta
PLCB2 | phospholipase C beta 2
GNAQ | G protein subunit alpha q
HSPB1 | heat shock protein family B (small) member 1
RELA | RELA proto−oncogene, NF−kB subunit
NOS2 | nitric oxide synthase 2
PIK3CG | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit gamm
TLR2 | toll like receptor 2
IL1R2 | interleukin 1 receptor type 2
PIK3CA | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit alpha
TNF | tumor necrosis factor
PRKACB | protein kinase cAMP−activated catalytic subunit beta
COL24A1 | collagen type XXIV alpha 1 chain
IL12A | interleukin 12A
PLCB4 | phospholipase C beta 4
PRKCG | protein kinase C gamma
IL12B | interleukin 12B
RAB5A | RAB5A, member RAS oncogene family
ACTN3 | actinin alpha 3 (gene/pseudogene)
PRKACG | protein kinase cAMP−activated catalytic subunit gamma
LAMA1 | laminin subunit alpha 1
PIK3R2 | phosphoinositide−3−kinase regulatory subunit 2
C8G | complement C8 gamma chain
GNA15 | G protein subunit alpha 15
COL2A1 | collagen type II alpha 1 chain

CA　　SLC　　SS

Infectious disease

Color Key
and Histogram

Count

**Tuberculosis
hsa05152**

TGFB1 | transforming growth factor beta 1
MR1 | major histocompatibility complex, class I-related
CLEC4M | mannose receptor, C type
MAPK3 | mitogen-activated protein kinase 3
RIPK3 | receptor-interacting serine-threonine kinase 3
IL12B | interleukin 12B
ITGB2 | integrin subunit beta 2
SFTPA1 | surfactant protein A1
STAT1 | signal transducer and activator of transcription 1
SCARB1 | scavenger receptor class B member 1
CCR5 | C-C motif chemokine receptor 5
RAB5C | RAB5C, member RAS oncogene family
BAD | BCL2 associated agonist of cell death
CASP10 | caspase 10
TGFB2 | transforming growth factor beta 2
ITGAM | integrin subunit alpha M
CAMK2G | calcium/calmodulin dependent protein kinase II gamma
NFKB1 | nuclear factor kappa B subunit 1
MAPK1 | mitogen-activated protein kinase 1
BAX | BCL2 associated X, apoptosis regulator
TLR1 | toll like receptor 1
SYK | spleen associated tyrosine kinase
TNFRSF1A | TNF receptor superfamily member 1A
ITPR1 | inositol 1,4,5-trisphosphate receptor type 1
TCIRG1 | T cell immune regulator 1, ATPase H+ transporting V0 subunit a3
IL18R1 | interleukin 18 receptor 1
TGFB3 | transforming growth factor beta 3
CLEC7A | C-type lectin domain containing 7A
IFNGR2 | interferon gamma receptor 2
APAF1 | apoptotic peptidase activating factor 1
SRC | SRC proto-oncogene, non-receptor tyrosine kinase
SPP1 | secreted phosphoprotein 1
IRAK2 | interleukin 1 receptor associated kinase 2
CLEC4E | C-type lectin domain family 4 member E
CASP8 | caspase 8
BCL10 | BCL10, immune signaling adaptor
VDR | vitamin D receptor
RELA | RELA proto-oncogene, NF-kB subunit
EP300 | E1A binding protein p300
NOS2 | nitric oxide synthase 2
RHOA | ras homolog family member A
ITGAX | integrin subunit alpha X
FCGR1A | Fc fragment of IgG receptor Ia
FCGR2B | Fc fragment of IgG receptor IIb
ATP6V0B | ATPase H+ transporting V0 subunit b
CEBPG | CCAAT enhancer binding protein gamma
CLEC6A | C-type lectin domain family 6 member A
MAPK11 | mitogen-activated protein kinase 11
RIPK1 | receptor interacting serine/threonine kinase 1
FADD | Fas associated via death domain
FAS | Fas cell surface death receptor
RAB7B | RAB7B, member RAS oncogene family
ARHGEF12 | Rho guanine nucleotide exchange factor 12
ATP6V0D1 | ATPase H+ transporting V0 subunit d1
CTSS | cathepsin S
PPP3R1 | protein phosphatase 3 regulatory subunit B, alpha
MAPK14 | mitogen-activated protein kinase 14
MAVS | mitochondrial antiviral signaling protein
TLR2 | toll like receptor 2
IL6R | interleukin 6 receptor
TNFRSF1B | TNF receptor superfamily member 1B
RFXANK | regulatory factor X associated ankyrin containing protein
ATP6AP1 | ATPase H+ transporting accessory protein 1
CAMP | cathelicidin antimicrobial peptide
LAMP1 | lysosomal associated membrane protein 1
ATP6V0C | ATPase H+ transporting V0 subunit c
NFKB2 | nuclear factor kappa B subunit 2
IL1B | interleukin 1 beta
MALT1 | MALT1 paracaspase
MAPK12 | mitogen-activated protein kinase 12
CARD9 | caspase recruitment domain family member 9
BID | BH3 interacting domain death agonist
CASP3 | caspase 3
ATP6V1H | ATPase H+ transporting V1 subunit H
FCGR1B | Fc fragment of IgG receptor Ib
IL23A | interleukin 23 subunit alpha
RAB5A | RAB5A, member RAS oncogene family
MYD88 | myeloid differentiation primary response 88
IRF1 | interferon regulatory factor 1
IL4 | interleukin 4
IRAK4 | interleukin 1 receptor associated kinase 4
TLR4 | toll like receptor 4
IFNA2 | interferon alpha 2
PPP3R2 | protein phosphatase 3 regulatory subunit B, beta
MAPK13 | mitogen-activated protein kinase 13
IFNA13 | interferon alpha 13
IFNB1 | interferon beta 1
LBP | lipopolysaccharide binding protein
NOD2 | nucleotide binding oligomerization domain containing 2
CALML3 | calmodulin like 3

CA
SLC
SS

Infectious disease

**Color Key
and Histogran**

Count

−1.5   0   1
Value

Hepatitis C
hsa05160

CLDN5 | claudin 5
CLDN4 | claudin 4
NFKBIA | NF-kB inhibitor alpha
MAPK3 | mitogen-activated protein kinase 3
IRF9 | interferon regulatory factor 9
OAS3 | 2'-5'-oligoadenylate synthetase 3
STAT1 | signal transducer and activator of transcription 1
PIK3CD | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
GRB2 | growth factor receptor bound protein 2
CLDN18 | claudin 18
NFKB1 | nuclear factor kappa B subunit 1
IRF3 | interferon regulatory factor 7
MAPK11 | mitogen-activated protein kinase 11
MRAS | muscle RAS oncogene homolog
NRAS | NRAS proto-oncogene, GTPase
TNFRSF1A | TNF receptor superfamily member 1A
RIPK1 | receptor interacting serine/threonine kinase 1
CLDN23 | claudin 23
PIK3CB | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta
PIK3R5 | phosphoinositide-3-kinase regulatory subunit 5
PPP2CB | protein phosphatase 2 catalytic subunit beta
NR1H3 | nuclear receptor subfamily 1 group H member 3
IFNAR2 | interferon alpha and beta receptor subunit 2
TICAM1 | toll like receptor adaptor molecule 1
CLDN1 | claudin 1
SCARB1 | scavenger receptor class B member 1
RELA | RELA proto-oncogene, NF-kB subunit
EIF2AK2 | eukaryotic translation initiation factor 2 alpha kinase 2
IKBKE | inhibitor of nuclear factor kappa B kinase subunit epsilon
IRF5 | interferon regulatory factor 5
EGFR | epidermal growth factor receptor
AXL | AXL receptor tyrosine kinase
AKT2 | AKT serine/threonine kinase 2
PIK3CG | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma
OAS1 | 2'-5'-oligoadenylate synthetase 1
PSME3 | proteasome activator subunit 3
IKBKG | inhibitor of nuclear factor kappa B kinase subunit gamma
MAPK1 | mitogen-activated protein kinase 1
STAT3 | signal transducer and activator of transcription 3
PPP2CA | protein phosphatase 2 catalytic subunit alpha
IFNAR1 | interferon alpha and beta receptor subunit 1
RASGRF1 | Ras protein specific guanine nucleotide releasing factor 1
BAD | BCL2 associated agonist of cell death
PIAS1 | protein inhibitor of activated STAT 1
PIK3CA | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
MAP2K1 | mitogen-activated protein kinase kinase 1
TNF | tumor necrosis factor
MAVS | mitochondrial antiviral signaling protein
GSK3B | glycogen synthase kinase 3 beta
PDPK1 | 3-phosphoinositide dependent protein kinase 1
PPARA | peroxisome proliferator activated receptor alpha
CLDN11 | claudin 11
MAPK12 | mitogen-activated protein kinase 12
TBK1 | TANK binding kinase 1
CLDN2 | claudin 2
EGF | epidermal growth factor
PPP2R2A | protein phosphatase 2 regulatory subunit Balpha
CLDN6 | claudin 6
KRAS | KRAS proto-oncogene, GTPase
IKBKB | inhibitor of nuclear factor kappa B kinase subunit epsilon
IFNA5 | interferon alpha 5
IFNA21 | interferon alpha 21
MAPK13 | mitogen-activated protein kinase 13
IFNB1 | interferon beta 1
BRAF | B-Raf proto-oncogene, serine/threonine kinase
CLDN7 | claudin 7
EIF2AK1 | eukaryotic translation initiation factor 2 alpha kinase 1
PIK3R2 | phosphoinositide-3-kinase regulatory subunit 2
CLDN14 | claudin 14
PPP2R2C | protein phosphatase 2 regulatory subunit Bgamma
CLDN9 | claudin 9

CA   SLC   SS

Infectious disease

Color Key and Histogran

Count

Hepatitis B hsa05161

TGFB1 | transforming growth factor beta 1
MMP9 | matrix metallopeptidase 9
NFKBIA | NFKB inhibitor alpha
MAPK3 | mitogen-activated protein kinase 3
STAT5A | signal transducer and activator of transcription 5A
STAT1 | signal transducer and activator of transcription 1
BCL2 | BCL2, apoptosis regulator
PIK3CD | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
CASP10 | caspase 10
GRB2 | growth factor receptor bound protein 2
YWHAB | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein beta
RBPTOHB | transcriptional corepressor 1
STAT6 | signal transducer and activator of transcription 6
NFKB1 | nuclear factor kappa B subunit 1
STAT5B | signal transducer and activator of transcription 5B
TLR3 | toll like receptor 3
DDX2 | apoptosis regulator
IRF7 | interferon regulatory factor 7
HRAS | HRas proto-oncogene, GTPase
JAK1 | Janus kinase 1
PTK2B | protein tyrosine kinase 2 beta
PIK3R3 | phosphoinositide-3-kinase regulatory subunit 3
PIK3CB | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta
NFATC4 | nuclear factor of activated T cells 4
BIRC3 | baculoviral IAP repeat containing 3
TGFB3 | transforming growth factor beta 3
YWHAZ | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta
CREB3 | cAMP responsive element binding protein 3
SRC | SRC proto-oncogene, non-receptor tyrosine kinase
CRKL | Crk like receptor adaptor molecule 1
CREB3L2 | cAMP responsive element binding protein 3 like 2
RELA | RELA proto-oncogene, NF-kB subunit
EP300 | E1A binding protein p300
CHUK | conserved helix-loop-helix ubiquitous kinase
PIK3CG | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma
PTEN | phosphatase and tensin homolog
IKBKG | inhibitor of nuclear factor kappa B kinase subunit gamma
MAPK1 | mitogen-activated protein kinase 1
FADD | Fas associated via death domain
STAT3 | signal transducer and activator of transcription 3
IFNAR1 | interferon alpha and beta receptor subunit 1
BAD | BCL2 associated agonist of cell death
CDK2 | cyclin dependent kinase 2
PIK3CA | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
CREB5 | cAMP responsive element binding protein 5
MAP2K1 | mitogen-activated protein kinase kinase 1
SMAD4 | SMAD family member 4
NFATC1 | nuclear factor
ATP6AP1 | ATPase H+ transporting accessory protein 1
MAVS | mitochondrial antiviral signaling protein
CREBBP | CREB binding protein
MAP2K7 | mitogen-activated protein kinase kinase 7
LAMTOR5 | late endosomal/lysosomal adaptor, MAPK and MTOR activator 5
MAP2K2 | mitogen-activated protein kinase kinase 2
TRAF | TRAF binding kinase
CRADD | CASP2 and RIPK1 domain containing adaptor protein
PRKCG | protein kinase C gamma
KRAS | KRAS proto-oncogene, GTPase
MYD88 | myeloid differentiation primary response 88
IKBKE | inhibitor of nuclear factor kappa B kinase subunit epsilon
IFNA21 | interferon alpha 21
IFNB1 | interferon beta 1
PIK3R2 | phosphoinositide-3-kinase regulatory subunit 2

CA   SLC   SS

Infectious disease

**Color Key
and Histogram**

Count

0 3

−0.5　0.5
Value

Vitamin digestion and absorption
hsa04977

TCN2 | transcobalamin 2

SCARB1 | scavenger receptor class B member 1

SLC46A1 | solute carrier family 46 member 1

SLC52A3 | solute carrier family 52 member 3

PLB1 | phospholipase B1

CUBN | cubilin

SLC19A1 | solute carrier family 19 member 1

GIF | gastric intrinsic factor

MMACHC | methylmalonic aciduria (cobalamin deficien

SLC19A2 | solute carrier family 19 member 2

APOA4 | apolipoprotein A4

CA　SLC　SS

Other

**Color Key
and Histogran**

Count

0   10

−1   0   1

Value

Morphine addiction
hsa05032

ADCY4 | adenylate cyclase 4
PRKCB | protein kinase C beta
ADCY3 | adenylate cyclase 3
GNAI2 | G protein subunit alpha i2
GNG2 | G protein subunit gamma 2
PDE3A | phosphodiesterase 3A
GNG12 | G protein subunit gamma 12
ARRB1 | arrestin beta 1
GRK6 | G protein−coupled receptor kinase 6
GABRD | gamma−aminobutyric acid type A receptor delta subunit
GNB4 | G protein subunit beta 4
ARRB2 | arrestin beta 2
GRK2 | G protein−coupled receptor kinase 2
ADCY6 | adenylate cyclase 6
GNB1 | G protein subunit beta 1
GRK3 | G protein−coupled receptor kinase 3
PDE3B | phosphodiesterase 3B
PDE7B | phosphodiesterase 7B
GNG8 | G protein subunit gamma 8
GNG5 | G protein subunit gamma 5
GNB2 | G protein subunit beta 2
GNAI1 | G protein subunit alpha i1
GNAI3 | G protein subunit alpha i3
GABBR1 | gamma−aminobutyric acid type B receptor subunit 1
GNG7 | G protein subunit gamma 7
PRKACB | protein kinase cAMP−activated catalytic subunit beta
GNGT1 | G protein subunit gamma transducin 1
GABRA3 | gamma−aminobutyric acid type A receptor alpha3 subunit
GABRQ | gamma−aminobutyric acid type A receptor theta subunit
GABRR1 | gamma−aminobutyric acid type A receptor rho1 subunit
ADORA1 | adenosine A1 receptor
PRKCG | protein kinase C gamma
PDE10A | phosphodiesterase 10A
GABRR2 | gamma−aminobutyric acid type A receptor rho2 subunit
GABRB1 | gamma−aminobutyric acid type A receptor beta1 subunit
KCNJ6 | potassium voltage−gated channel subfamily J member 6
GABRG2 | gamma−aminobutyric acid type A receptor gamma2 subunit
OPRM1 | opioid receptor mu 1
PRKACG | protein kinase cAMP−activated catalytic subunit gamma
GABRG3 | gamma−aminobutyric acid type A receptor gamma3 subunit
KCNJ9 | potassium voltage−gated channel subfamily J member 9
GNB3 | G protein subunit beta 3
GABBR2 | gamma−aminobutyric acid type B receptor subunit 2
GNG13 | G protein subunit gamma 13
GNG4 | G protein subunit gamma 4

CA   SLC   SS

Other

Ribosome biogenesis in eukaryotes
hsa03008

XRN1 | 5'–3' exoribonuclease 1

HEATR1 | HEAT repeat containing 1

POP4 | POP4 homolog, ribonuclease P/MRP subunit

NOP10 | NOP10 ribonucleoprotein

XRN2 | 5'–3' exoribonuclease 2

RPP25 | ribonuclease P and MRP subunit p25

TCOF1 | treacle ribosome biogenesis factor 1

EIF6 | eukaryotic translation initiation factor 6

NXT2 | nuclear transport factor 2 like export factor 2

CSNK2A1 | casein kinase 2 alpha 1

CSNK2B | casein kinase 2 beta

POP7 | POP7 homolog, ribonuclease P/MRP subunit

GNL3L | G protein nucleolar 3 like

REXO2 | RNA exonuclease 2

CA   SLC   SS

Other

**Color Key
and Histogram**

Count

0 6

−1   1

Value

p53 signaling pathway
hsa04115

SERPINE1 | serpin family E member 1
CCND2 | cyclin D2
CCND3 | cyclin D3
CCNB2 | cyclin B2
BAX | BCL2 associated X, apoptosis regulator
FAS | Fas cell surface death receptor
CDKN2A | cyclin dependent kinase inhibitor 2A
CDK1 | cyclin dependent kinase 1
PPM1D | protein phosphatase, Mg2+/Mn2+ dependent 1D
CCNB1 | cyclin B1
APAF1 | apoptotic peptidase activating factor 1
GTSE1 | G2 and S−phase expressed 1
CASP8 | caspase 8
CD82 | CD82 molecule
RRM2 | ribonucleotide reductase regulatory subunit M2
THBS1 | thrombospondin 1
RFWD2 | ring finger and WD repeat domain 2
PTEN | phosphatase and tensin homolog
SERPINB5 | serpin family B member 5
TP53l3 | tumor protein p53 inducible protein 3
TP73 | tumor protein p73
CCNE1 | cyclin E1
CDK2 | cyclin dependent kinase 2
MDM2 | MDM2 proto−oncogene
CHEK1 | checkpoint kinase 1
RCHY1 | ring finger and CHY zinc finger domain containing 1
SESN2 | sestrin 2
BID | BH3 interacting domain death agonist
ADGRB1 | adhesion G protein−coupled receptor B1
SFN | stratifin
CCNG1 | cyclin G1
CCNE2 | cyclin E2
MDM4 | MDM4, p53 regulator
ZMAT3 | zinc finger matrin−type 3
SHISA5 | shisa family member 5
SESN3 | sestrin 3
TSC2 | TSC complex subunit 2
CCNB3 | cyclin B3
SESN1 | sestrin 1
STEAP3 | STEAP3 metalloreductase

CA SLC SS

Other

**Glycerophospholipid metabolism
hsa00564**

PLA2G4A | phospholipase A2 group IVA
ACHE | acetylcholinesterase (Cartwright blood group)
CHKA | choline kinase alpha
LPCAT2 | lysophosphatidylcholine acyltransferase 2
AGPAT4 | 1–acylglycerol–3–phosphate O–acyltransferase 4
PNPLA6 | patatin like phospholipase domain containing 6
PGS1 | phosphatidylglycerophosphate synthase 1
CDS2 | CDP–diacylglycerol synthase 2
PLA2G2D | phospholipase A2 group IID
GPCPD1 | glycerophosphocholine phosphodiesterase 1
PCYT1A | phosphate cytidylyltransferase 1, choline, alpha
CDS1 | CDP–diacylglycerol synthase 1
DGKH | diacylglycerol kinase eta
LPGAT1 | lysophosphatidylglycerol acyltransferase 1
AGPAT1 | 1–acylglycerol–3–phosphate O–acyltransferase 1
PLA2G12B | phospholipase A2 group XIIB
PLD2 | phospholipase D2
PLD1 | phospholipase D1
PLA2G15 | phospholipase A2 group XV
PISD | phosphatidylserine decarboxylase
TAZ | tafazzin
PTDSS2 | phosphatidylserine synthase 2
CEPT1 | choline/ethanolamine phosphotransferase 1
PLB1 | phospholipase B1
GPAT4 | glycerol–3–phosphate acyltransferase 4
DGKG | diacylglycerol kinase gamma
GPD2 | glycerol–3–phosphate dehydrogenase 2
MBOAT7 | membrane bound O–acyltransferase domain containing 7
ETNK1 | ethanolamine kinase 1
LYPLA2 | lysophospholipase II
DGKI | diacylglycerol kinase iota
PCYT1B | phosphate cytidylyltransferase 1, choline, beta
GPD1L | glycerol–3–phosphate dehydrogenase 1 like
PHOSPHO1 | phosphoethanolamine/phosphocholine phosphatase
PCYT2 | phosphate cytidylyltransferase 2, ethanolamine
MBOAT1 | membrane bound O–acyltransferase domain containing 1
PLA2G2F | phospholipase A2 group IIF
GPAM | glycerol–3–phosphate acyltransferase, mitochondrial
AGPAT3 | 1–acylglycerol–3–phosphate O–acyltransferase 3
SELENOI | selenoprotein I
LPCAT3 | lysophosphatidylcholine acyltransferase 3
CRLS1 | cardiolipin synthase 1
LPIN1 | lipin 1
PLA2G12A | phospholipase A2 group XIIA
PNPLA7 | patatin like phospholipase domain containing 7
LYPLA1 | lysophospholipase I
PEMT | phosphatidylethanolamine N–methyltransferase
LPIN2 | lipin 2
MBOAT2 | membrane bound O–acyltransferase domain containing 2
ETNK2 | ethanolamine kinase 2

CA   SLC   SS

Other

**Color Key
and Histogran**

Dorso−ventral axis formation
hsa04320

NOTCH4 | notch 4

ETS2 | ETS proto−oncogene 2, transcription factor

MAPK3 | mitogen−activated protein kinase 3

GRB2 | growth factor receptor bound protein 2

NOTCH1 | notch 1

ETV7 | ETS variant 7

PIWIL4 | piwi like RNA−mediated gene silencing 4

NOTCH3 | notch 3

EGFR | epidermal growth factor receptor

SPIRE2 | spire type actin nucleation factor 2

ETV6 | ETS variant 6

SPIRE1 | spire type actin nucleation factor 1

MAPK1 | mitogen−activated protein kinase 1

SOS1 | SOS Ras/Rac guanine nucleotide exchange factor 1

NOTCH2 | notch 2

MAP2K1 | mitogen−activated protein kinase kinase 1

PIWIL2 | piwi like RNA−mediated gene silencing 2

KRAS | KRAS proto−oncogene, GTPase

PIWIL1 | piwi like RNA−mediated gene silencing 1

CA SLC SS

Other

Osteoclast differentiation
hsa04380

SIRPA | signal regulatory protein alpha
TGFBR2 | transforming growth factor beta receptor 2
IFNGR1 | interferon gamma receptor 1
NFKBIA | NF-kappa-B inhibitor alpha
CYBB | cytochrome b-245 alpha chain
TREM2 | triggering receptor expressed on myeloid cells 2
CSF1 | colony stimulating factor 1
MAPK3 | mitogen-activated protein kinase 3
NFKB2 | nuclear factor kappa B subunit 2
PPARG | peroxisome proliferator-activated receptor gamma
STAT1 | signal transducer and activator of transcription 1
FOSL1 | FOS like 1, AP-1 transcription factor subunit
TNFRSF11A | TNF receptor superfamily member 11a
PIK3CD | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
NCF2 | neutrophil cytosolic factor 2
RELB | RELB proto-oncogene, NF-kB subunit
TGFB2 | transforming growth factor beta 2
PLCG2 | phospholipase C gamma 2
FYN | FYN proto-oncogene
GAB2 | GRB2 associated binding protein 2
SOCS3 | suppressor of cytokine signaling 3
LCP2 | lymphocyte cytosolic protein 2
NFATC1 | nuclear factor of activated T cells 1
MAPKAPK2 | MAPK activated protein kinase 2
MAP2K1 | spleen associated tyrosine binding protein
MAPK11 | mitogen-activated protein kinase 11
TNFRSF1A | TNF receptor superfamily member 1A
JAK1 | Janus kinase 1
LILRB4 | leukocyte immunoglobulin like receptor B4
PIK3CB | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta
TYROBP | TYRO protein tyrosine kinase binding protein
PIK3R5 | phosphoinositide-3-kinase regulatory subunit 5
IL1B | interleukin 1 beta
IFNGR2 | interferon gamma receptor 2
IL1R1 | interleukin 1 receptor type 1
MAP2K6 | mitogen-activated protein kinase kinase 6
PPP3CA | protein phosphatase 3 catalytic subunit alpha
TGFBR1 | transforming growth factor beta receptor 1
RELA | RELA proto-oncogene, NF-kB subunit
CHUK | conserved helix-loop-helix ubiquitous kinase
PIK3CG | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma
RAC1 | Rac family small GTPase 1
SYK | tyrosine kinase
TGFB3 | transforming growth factor beta 3
LILRB1 | leukocyte immunoglobulin like receptor B1
LILRB2 | leukocyte immunoglobulin like receptor B2
IKBKG | inhibitor of nuclear factor kappa B kinase subunit gamma
MAP2K1 | mitogen-activated protein kinase kinase 1
OSCAR | osteoclast associated immunoglobulin like receptor
LILRA5 | leukocyte immunoglobulin like receptor A5
PPP3R1 | protein phosphatase 3 regulatory subunit B, alpha
PIK3CA | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
MAP3K14 | mitogen-activated protein kinase 14
TNF | tumor necrosis factor
NCF1 | neutrophil cytosolic factor 1
NOX1 | NADPH oxidase 1
CYBA | cytochrome b-245 alpha chain
MAP2K1 | mitogen-activated protein kinase kinase 1
LILRA6 | leukocyte immunoglobulin like receptor A6
MAPK12 | mitogen-activated protein kinase 12
TNFSF11 | TNF superfamily member 11
LILRA1 | leukocyte immunoglobulin like receptor A1
FCGR2B | Fc fragment of IgG receptor IIb
IL1A | interleukin 1 alpha
PPP3R1 | protein phosphatase 3 regulatory subunit B, beta
NOX3 | NADPH oxidase 3
MAPK13 | mitogen-activated protein kinase 13
IL1B | interleukin 1 beta
PIK3R2 | phosphoinositide-3-kinase regulatory subunit 2
FES | Fes proto-oncogene, tyrosine kinase
BLNK | B-cell linker

CA SLC SS

Other

**Color Key
and Histogran**

Count

0 40

−2 0 2

Value

Focal adhesion
hsa04510

COL4A2 | collagen type IV alpha 2 chain
PAK2 | P21 (RAC1) activated kinase 2
ITGA5 | integrin subunit alpha 5
PIK3R1 | phosphoinositide-3-kinase regulatory subunit 1
COL4A1 | collagen type IV alpha 1 chain
ITGA6 | integrin subunit alpha 6
PPP1CB | protein phosphatase 1 catalytic subunit beta
LAMA4 | laminin subunit alpha 4
GRB2 | growth factor receptor bound protein 2
COL1A2 | collagen type I alpha 2 chain
VWF | von Willebrand factor
COL6A3 | collagen type VI alpha 3 chain
PARVA | parvin alpha
CAV1 | caveolin 1
LAMC1 | laminin subunit gamma 1
HGF | hepatocyte growth factor
PDGFB | platelet derived growth factor subunit B
VEGFC | vascular endothelial growth factor C
EGFR | epidermal growth factor receptor
VASP | vasodilator stimulated phosphoprotein
MYL9 | myosin light chain 9
MAPK3 | mitogen-activated protein kinase 3
PPP1CC | protein phosphatase 1 catalytic subunit gamma
ITGB1 | integrin subunit beta 1
PDGFC | platelet derived growth factor C
COL27A1 | collagen type XXVII alpha 1 chain
ITGA1 | integrin subunit alpha 1
ROCK2 | Rho associated coiled-coil containing protein kinase 2
PIK3CD | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
CRK | CRK proto-oncogene, adaptor protein
GRB2 | growth factor receptor bound protein 2
MAPK1 | mitogen-activated protein kinase 1
ITGA2B | integrin subunit alpha 2b
RAC1 | Rac family small GTPase 1
BRAF | B-Raf proto-oncogene, serine/threonine kinase
PPP1R12C | protein phosphatase 1 regulatory subunit 12C
PAK1 | p21 (RAC1) activated kinase 1
VEGFA | vascular endothelial growth factor A
COL5A1 | collagen type V alpha 1 chain
MYLK | myosin light chain kinase
ITGB5 | integrin subunit beta 5
ROCK1 | Rho associated coiled-coil containing protein kinase 1
PIK3CB | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta
ARHGEF1 | Rho guanine nucleotide exchange factor 1
PIK3R5 | phosphoinositide-3-kinase regulatory subunit 5
PDGFRB | platelet derived growth factor receptor beta
MET | MET proto-oncogene, receptor tyrosine kinase
BIRC2 | baculoviral IAP repeat containing 2
BIRC3 | baculoviral IAP repeat containing 3
XIAP | X-linked inhibitor of apoptosis
CDC42 | cell division cycle 42
SRC | SRC proto-oncogene, non-receptor tyrosine kinase
FLT1 | fms related receptor tyrosine kinase 1
PRKCA | protein kinase C alpha
RAP1A | RAP1A, member of RAS oncogene family
PIK3CA | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PTEN | phosphatase and tensin homolog
MAPK8 | mitogen-activated protein kinase 8
MAP2K1 | mitogen-activated protein kinase kinase 1
ITGA10 | integrin subunit alpha 10
RAPGEF1 | Rap guanine nucleotide exchange factor 1
PIK3CG | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma
RHOA | ras homolog family member A
PDPK1 | 3-phosphoinositide dependent protein kinase 1
RAF1 | Raf-1 proto-oncogene, serine/threonine kinase
PAK4 | p21 (RAC1) activated kinase 4
PDGFD | platelet derived growth factor D
THBS2 | thrombospondin 2
PDGFC | platelet derived growth factor C
COL4A4 | collagen type IV alpha 4 chain
ABL1 | ABL proto-oncogene 1, non-receptor tyrosine kinase
PTK2 | protein tyrosine kinase 2
MYL10 | myosin light chain 10
RASGRF1 | Ras protein specific guanine nucleotide releasing factor 1
CAV3 | caveolin 3
MYL12A | myosin light chain 12A (gene/pseudogene)
PRKCB | protein kinase C beta
PAK6 | p21 (RAC1) activated kinase 6
PDGFRA | platelet derived growth factor receptor alpha
PPP1R12B | protein phosphatase 1 regulatory subunit 2
COL6A1 | collagen type VI alpha 1 chain
RAC3 | Rac family small GTPase 3

CA   SLC   SS

Other

**Color Key
and Histogran**

Count

−1.5　0　1

Value

Adherens junction
hsa04520

RAC2 | Rac family small GTPase 2
TGFBR2 | transforming growth factor beta receptor 2
TCF7L1 | transcription factor 7 like 1
SNAI1 | snail family transcriptional repressor 1
ACTN1 | actinin alpha 1
VCL | vinculin
MAPK3 | mitogen−activated protein kinase 3
SNAI2 | snail family transcriptional repressor 2
CTNNB1 | catenin beta 1
ACTN4 | actinin alpha 4
TCF7L2 | transcription factor 7 like 2
PTPN6 | protein tyrosine phosphatase, non−receptor type 6
ACTB | actin beta
PTPN1 | protein tyrosine phosphatase, non−receptor type 1
WASF2 | WAS protein family member 2
WAS | Wiskott−Aldrich syndrome
NECTIN2 | nectin cell adhesion molecule 2
IQGAP1 | IQ motif containing GTPase activating protein 1
MET | MET proto−oncogene, receptor tyrosine kinase
PTPRF | protein tyrosine phosphatase, receptor type F
CDC42 | cell division cycle 42
SRC | SRC proto−oncogene, non−receptor tyrosine kinase
INSR | insulin receptor
TGFBR1 | transforming growth factor beta receptor 1
EP300 | E1A binding protein p300
RHOA | ras homolog family member A
RAC1 | Rac family small GTPase 1
EGFR | epidermal growth factor receptor
MAPK1 | mitogen−activated protein kinase 1
FARP2 | FERM, ARH/RhoGEF and pleckstrin domain protein 2
PTPRJ | protein tyrosine phosphatase, receptor type J
CSNK2A1 | casein kinase 2 alpha 1
PARD3 | par−3 family cell polarity regulator
SMAD4 | SMAD family member 4
CTNNA1 | catenin alpha 1
CSNK2B | casein kinase 2 beta
CREBBP | CREB binding protein
LMO7 | LIM domain 7
WASL | Wiskott−Aldrich syndrome like
WASF1 | WAS protein family member 1
ACTG1 | actin gamma 1
ERBB2 | erb−b2 receptor tyrosine kinase 2
ACTN3 | actinin alpha 3 (gene/pseudogene)
BAIAP2 | BAI1 associated protein 2
RAC3 | Rac family small GTPase 3
NECTIN4 | nectin cell adhesion molecule 4

CA　SLC　SS

Other

**Color Key
and Histogram**

Count

−1　0　1
Value

Synaptic vesicle cycle
hsa04721

VAMP2 | vesicle associated membrane protein 2
AP2B1 | adaptor related protein complex 2 beta 1 subunit
TCIRG1 | T−cell immune regulator 1, ATPase H+ transporting V0 subunit a3
ATP6V1C1 | ATPase H+ transporting V1 subunit C1
ATP6V1E1 | ATPase H+ transporting V1 subunit E1
CPLX1 | complexin 1
AP2M1 | adaptor related protein complex 2 mu 1 subunit
DNM2 | dynamin 2
SYT1 | synaptotagmin 1
AP2A2 | adaptor related protein complex 2 alpha 2 subunit
ATP6V0A1 | ATPase H+ transporting V0 subunit a1
ATP6V0B | ATPase H+ transporting V0 subunit b
DNM1 | dynamin 1
CLTB | clathrin light chain B
CLTC | clathrin heavy chain
AP2A1 | adaptor related protein complex 2 alpha 1 subunit
ATP6V0E1 | ATPase H+ transporting V0 subunit e1
ATP6V1B2 | ATPase H+ transporting V1 subunit B2
NAPA | NSF attachment protein alpha
ATP6V0D1 | ATPase H+ transporting V0 subunit d1
STX1A | syntaxin 1A
SNAP25 | synaptosome associated protein 25
AP2S1 | adaptor related protein complex 2 sigma 1 subunit
ATP6V0C | ATPase H+ transporting V0 subunit c
DNM3 | dynamin 3
STX3 | syntaxin 3
CLTA | clathrin light chain A
ATP6V1A | ATPase H+ transporting V1 subunit A
ATP6V1H | ATPase H+ transporting V1 subunit H
SLC18A1 | solute carrier family 18 member A1
STX1B | syntaxin 1B
ATP6V1B1 | ATPase H+ transporting V1 subunit B1
SLC17A6 | solute carrier family 17 member 6
NSF | N−ethylmaleimide sensitive factor, vesicle fusing ATPase
RIMS1 | regulating synaptic membrane exocytosis 1
CLTCL1 | clathrin heavy chain like 1
ATP6V1F | ATPase H+ transporting V1 subunit F
UNC13A | unc−13 homolog A
SLC18A3 | solute carrier family 18 member A3
ATP6V1C2 | ATPase H+ transporting V1 subunit C2
ATP6V0E2 | ATPase H+ transporting V0 subunit e2

CA　SLC　SS

Other

Regulation of actin cytoskeleton
hsa04810

Color Key
and Histogram

Count

−1   1

Value

MYL9 | myosin light chain 9
PPP1R12B | protein phosphatase 1 regulatory subunit 12B
ITGB3 | integrin subunit beta 3
ITGA2 | integrin subunit alpha 3
FGFR4 | fibroblast growth factor receptor 4
ARHGEF6 | Rac/Cdc42 guanine nucleotide exchange factor 6
ARPC1B | actin related protein 2/3 complex subunit 1B
ACTN1 | actinin alpha 1
ACTG1 | actin gamma 1
ARPC5 | actin related protein 2/3 complex subunit 5
PIP5K1B | phosphatidylinositol-4-phosphate 5-kinase type 1 beta
GNA13 | G protein subunit alpha 13
ITGA7 | integrin subunit alpha 7
LIMK1 | LIM domain kinase 1
PIK3CD | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
MYL12B | myosin light chain 12B
CFL1 | cofilin 1
CYFIP2 | cytoplasmic FMR1 interacting protein 2
PPP1R12C | protein phosphatase 1 regulatory subunit 12C
DIAPH3 | diaphanous related formin 3
ARPC1A | actin related protein 2/3 complex subunit 1A
ACTB | actin beta
F2R | coagulation factor II thrombin receptor
GNG12 | G protein subunit gamma 12
ARPC4 | actin related protein 2/3 complex subunit 4
BAIAP2 | BAI1 associated protein 2
ITGA11 | integrin subunit alpha 11
PPP1R12A | protein phosphatase 1 regulatory subunit 12A
PIK3CB | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta
CHRM2 | cholinergic receptor muscarinic 2
MYH10 | myosin heavy chain 10
IQGAP1 | IQ motif containing GTPase activating protein 1
BRAF | B-Raf proto-oncogene, serine/threonine kinase
PFN2 | profilin 2
ARHGEF4 | Rho guanine nucleotide exchange factor 4
CRKL | CRK like proto-oncogene, adaptor protein
GSN | gelsolin
PDGFRA | platelet derived growth factor receptor alpha
PIK3R2 | phosphoinositide-3-kinase regulatory subunit 2 gamma
ARHGEF7 | Rho guanine nucleotide exchange factor 7
PIK3CA | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
FN1 | fibronectin 1
RRAS | RAS related
EZR | ezrin
BCAR1 | BCAR1 scaffold protein, Cas family member
PDGFC | platelet derived growth factor C
CHRM1 | cholinergic receptor muscarinic 1
PIK3CG | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma
DIAPH1 | diaphanous related formin 1
GNA12 | G protein subunit alpha 12
CHRM3 | cholinergic receptor muscarinic 3
PIP5K1C | phosphatidylinositol-4-phosphate 5-kinase type 2 alpha
SSH1 | slingshot protein phosphatase 1
ARHGEF12 | Rho guanine nucleotide exchange factor 12
ARHGEF1 | Rho guanine nucleotide exchange factor 1
PIP5K1A | phosphatidylinositol-4-phosphate 5-kinase type 1 alpha
FGF9 | fibroblast growth factor 9
MAP2K1 | mitogen-activated protein kinase kinase 1
ACTR2 | ARP2 actin related protein 2 homolog
ACTR3B | actin related protein 3B
BDKRB1 | bradykinin receptor B1
MYLK | myosin light chain kinase
NCKAP1 | NCK associated protein 1
DIAPH2 | diaphanous related formin 2
VAV3 | vav guanine nucleotide exchange factor 3
PDGFD | platelet derived growth factor D
FGF7 | fibroblast growth factor 7
GNA13 | G protein subunit alpha 13
CHRM4 | cholinergic receptor muscarinic 4
MSN | moesin
MYH9 | myosin heavy chain 9
INSRR | insulin receptor related receptor
NRAS | NRAS proto-oncogene, GTPase
BDKRB2 | bradykinin receptor B2
CHRM4 | cholinergic receptor muscarinic 4
ACTR3C | actin related protein 3C (pseudogene)
FGF17 | fibroblast growth factor 17
CHRM5 | cholinergic receptor muscarinic 5
FGF11 | fibroblast growth factor 11
RAF1 | Raf-1 proto-oncogene, serine/threonine kinase
PPP1CA | protein phosphatase 1 catalytic subunit alpha
SSH3 | slingshot protein phosphatase 3
TIAM1 | T cell lymphoma invasion and metastasis 1
PIK3R2 | phosphoinositide-3-kinase regulatory subunit 2
CFL2 | cofilin 2
EGFR | epidermal growth factor receptor
FGF1 | fibroblast growth factor 1
BAIAP2 | BAI1 associated protein 3
GNA12 | G protein subunit alpha 12
SDC1 | syndecan 1
RHOJ | ras homolog family member J
SDC4 | syndecan 4
RDX | radixin
CD14 | CD14 molecule
CRK | CRK proto-oncogene, adaptor protein
ITGA6 | integrin subunit alpha 6
BAIAP2L1 | BAR/IMD domain containing adaptor protein 2 like 1
BAIAP2 | BAI1 associated protein 2
SDIN | scinderin y small GTP ase 3

CA   SLC   SS

Color Key and Histogram

Count

Amyotrophic lateral sclerosis (ALS)
hsa05014

TNFRSF1B | TNF receptor superfamily member 1B
CASP1 | caspase 1
BCL2 | BCL2, apoptosis regulator
BAX | BCL2 associated X, apoptosis regulator
MAPK11 | mitogen−activated protein kinase 11
TNFRSF1A | TNF receptor superfamily member 1A
MAP2K6 | mitogen−activated protein kinase kinase 6
APAF1 | apoptotic peptidase activating factor 1
PPP3CA | protein phosphatase 3 catalytic subunit alpha
GRIN2D | glutamate ionotropic receptor NMDA type subunit 2D
RAC1 | Rac family small GTPase 1
BCL2L1 | BCL2 like 1
DERL1 | derlin 1
DAXX | death domain associated protein
BAD | BCL2 associated agonist of cell death
PPP3R1 | protein phosphatase 3 regulatory subunit B, alpha
MAPK14 | mitogen−activated protein kinase 14
TNF | tumor necrosis factor
GRIN2A | glutamate ionotropic receptor NMDA type subunit 2A
MAPK12 | mitogen−activated protein kinase 12
BID | BH3 interacting domain death agonist
GRIA1 | glutamate ionotropic receptor AMPA type subunit 1
RAB5A | RAB5A, member RAS oncogene family
TOMM40L | translocase of outer mitochondrial membrane 40 like
PPP3R2 | protein phosphatase 3 regulatory subunit B, beta
MAP3K5 | mitogen−activated protein kinase kinase kinase 5
MAPK13 | mitogen−activated protein kinase 13
GRIN2C | glutamate ionotropic receptor NMDA type subunit 2C
SOD1 | superoxide dismutase 1

CA   SLC   SS

Other

**Color Key
and Histogram**

Count

0 25

−1.5 0 1

Value

Alcoholism
hsa05034

PPP1R1B | protein phosphatase 1 regulatory inhibitor subunit 1B
MAPK3 | mitogen-activated protein kinase 3
SLC18A2 | solute carrier family 18 member A2
GNAI2 | G protein subunit alpha i2
GRB2 | growth factor receptor bound protein 2
GNG12 | G protein subunit gamma 12
HDAC7 | histone deacetylase 7
ARHGEF1 | Rho/Rac guanine nucleotide exchange factor
ADCY1 | adenylate cyclase 1
HIST1H2BK | histone cluster 1 H2B family member k
CAMKK2 | calcium/calmodulin dependent protein kinase kinase 2
NRAS | NRAS proto-oncogene, GTPase
H2AFX | H2A histone family member X
GNB4 | G protein subunit beta 4
ATF6B | activating transcription factor 6 beta
CREB3 | cAMP responsive element binding protein 3
PPP1CA | protein phosphatase 1 catalytic subunit alpha
CREB3L2 | cAMP responsive element binding protein 3 like 2
GRIN2D | glutamate ionotropic receptor NMDA type subunit 2D
HIST1H2BM | histone cluster 1 H2B family member m
BRAF | B-Raf proto-oncogene, serine/threonine kinase
H2AFV | H2A histone family member V
HDAC5 | histone deacetylase 5
HIST1H2BD | histone cluster 1 H2B family member d
HIST1H2BH | histone cluster 1 H2B family member e
MAPK1 | mitogen-activated protein kinase 1
GNG8 | G protein subunit gamma 8
CAMKK1 | calcium/calmodulin dependent protein kinase kinase 1
SOS2 | SOS Ras/Rac guanine nucleotide exchange factor 1
CREB5 | cAMP responsive element binding protein 5
GNAI1 | G protein subunit alpha i1
GNAI3 | G protein subunit alpha i3
H2AFZ | H2A histone family member Z
GNG3 | G protein subunit gamma 3
H3A3A | H3 histone family member 3A
H3F3A | H3 histone family member 3A
GRIN2A | glutamate ionotropic receptor NMDA type subunit 2A
MAP2K1 | mitogen-activated protein kinase kinase 1
GNG11 | G protein subunit gamma 11
HIST1H2BC | histone cluster 1 H2B family member h
HIST1H2BC | histone cluster 1 H2B family member c
HDAC8 | histone deacetylase 8
GRIN3A | glutamate ionotropic receptor NMDA type subunit 3A
GRIN3B | glutamate ionotropic receptor NMDA type subunit 3B
SLC6A3 | solute carrier family 6 member 3
HIST1H2BO | histone cluster 1 H2B family member o
ADORA2A | adenosine A2a receptor
KRAS | KRAS proto-oncogene, GTPase
PRKAR1A | cAMP-dependent protein kinase inhibitor alpha
SLC18A1 | solute carrier family 18 member A1
HIST2H2AA3 | histone cluster 2 H2A family member a3
BRAF | B-Raf proto-oncogene, serine/threonine kinase
GRIN2C | glutamate ionotropic receptor NMDA type subunit 2C
HIST3H3 | histone cluster 3 H3
HIST1H2AB | histone cluster 1 H2A family member b
HIST1H3E | histone cluster 1 H3 family member e
GNB2 | G protein subunit beta 2
DRD2 | dopamine receptor D2
GNG13 | G protein subunit gamma 13
HIST1H2AI | histone cluster 1 H2A family member i
HIST1H2AM | histone cluster 1 H2A family member m
H2AFY2 | H2A histone family member Y2
DDC | dopa decarboxylase
GNG4 | G protein subunit gamma 4
HIST3H2A | histone cluster 3 H2A
CALML3 | calmodulin like 3

CA   SLC   SS

Other

**Color Key
and Histogran**

Value

**Primary immunodeficiency
hsa05340**

IL2RG | interleukin 2 receptor subunit gamma

TAP1 | transporter 1, ATP binding cassette subfamily B mer

PTPRC | protein tyrosine phosphatase, receptor type C

TAP2 | transporter 2, ATP binding cassette subfamily B mer

JAK3 | Janus kinase 3

BTK | Bruton tyrosine kinase

IKBKG | inhibitor of nuclear factor kappa B kinase subunit g

RFXANK | regulatory factor X associated ankyrin containing

DCLRE1C | DNA cross−link repair 1C

TNFRSF13B | TNF receptor superfamily member 13B

AICDA | activation induced cytidine deaminase

RAG2 | recombination activating 2

BLNK | B−cell linker

CA   SLC   SS

Other

**Color Key
and Histogram**

Count

0   60

−3   0   2

Value

MAPK signaling pathway
hsa04010

RAC2 | Rac family small GTPase 2
TGFB2 | transforming growth factor beta 1
TGFBR2 | transforming growth factor beta receptor 2
PDGFRB | platelet derived growth factor receptor beta
FGFR1 | platelet derived growth factor subunit B
MAP3K8 | mitogen-activated protein kinase kinase kinase 8
STK3 | serine/threonine kinase 3
MAP3K20 | mitogen-activated protein kinase kinase kinase 20
CHUK | conserved helix-loop-helix ubiquitous kinase
IKBKB | inhibitor of nuclear factor kappa B kinase subunit beta
RELB | RELB proto-oncogene, NF-kB subunit
FOS | Fos proto-oncogene, AP-1 transcription factor subunit
RASGRF1 | Ras protein specific guanine nucleotide releasing factor 1
MEF2C | myocyte enhancer factor 2C
MAP3K12 | mitogen-activated protein kinase kinase kinase 11
NFATC2 | nuclear factor of activated T cells 2
PTPN7 | protein tyrosine phosphatase, non-receptor type 7
MRAS | muscle RAS oncogene homolog
RAP1A | RAP1A, member of RAS oncogene family
RASGRP3 | RAS guanyl releasing protein 3
MAP3K3 | mitogen-activated protein kinase kinase kinase 3
GRAP | GRB2 related adaptor protein
GRB2 | growth factor receptor bound protein 2
TGFB3 | transforming growth factor beta 3
MAP3K4 | mitogen-activated protein kinase kinase kinase 4
STK4 | serine/threonine kinase 4
MAP4K1 | mitogen-activated protein kinase kinase kinase kinase 1
PLA2G4A | phospholipase A2 group IVA
PRKCB | protein kinase C beta
MAP4K3 | mitogen-activated protein kinase kinase kinase kinase 13
IGF1R | insulin like growth factor 1 receptor
MAP3K6 | mitogen-activated protein kinase kinase kinase 6
CACNA1D | calcium voltage-gated channel subunit alpha1 D
MAP2K2 | mitogen-activated protein kinase kinase 2
MAP2K7 | mitogen-activated protein kinase kinase 7
FAS | Fas cell surface death receptor
RAC3 | Rac family small GTPase 3
ARRB2 | arrestin beta 2
RASGRF2 | Ras protein specific guanine nucleotide exchange factor 2
IKBKG | inhibitor of nuclear factor kappa B kinase subunit gamma
CACNB1 | calcium voltage-gated channel auxiliary subunit beta 1
NGFR | nerve growth factor receptor
MAPKAPK2 | mitogen-activated protein kinase-activated protein kinase 2
DUSP10 | dual specificity phosphatase 10
ELK4 | ETS transcription factor ELK4
TP53 | tumor protein p53
PPP3CA | protein phosphatase 3 catalytic subunit alpha
MAP2K1 | mitogen-activated protein kinase kinase 1
TAOK2 | TAO kinase 2
PPM1A | protein phosphatase, Mg2+/Mn2+ dependent 1A
HSPA1A | heat shock protein family A (Hsp70) member 1A
HSPA1L | heat shock protein family A (Hsp70) member 1 like
PRKACB | protein kinase cAMP-activated catalytic subunit beta
MAP2K5 | mitogen-activated protein kinase kinase 5
MAPK7 | mitogen-activated protein kinase 7
MAPK15 | mitogen-activated protein kinase 15
GADD45A | growth arrest and DNA damage inducible alpha
CACNA1F | calcium voltage-gated channel subunit alpha1 F
CACNG3 | calcium voltage-gated channel auxiliary subunit gamma 3
RAPGEF2 | Rap guanine nucleotide exchange factor 2
CACNG6 | calcium voltage-gated channel auxiliary subunit gamma 6
CACNG8 | calcium voltage-gated channel auxiliary subunit gamma 8
HSPB1 | heat shock protein family B (small) member 1
FGF20 | fibroblast growth factor 20
CACNG1 | calcium voltage-gated channel auxiliary subunit gamma 1
CACNG2 | calcium voltage-gated channel auxiliary subunit gamma 2
ADRA1A | adrenoceptor alpha 1A
MAP2K6 | mitogen-activated protein kinase kinase 6
PRKACG | protein kinase cAMP-activated catalytic subunit gamma
CACNG7 | calcium voltage-gated channel auxiliary subunit gamma 7
DAXX | death domain associated protein
CACNA2D2 | calcium voltage-gated channel auxiliary subunit alpha2delta 2
CACNA2D3 | calcium voltage-gated channel auxiliary subunit alpha2delta 3
HSPA6 | heat shock protein family A (Hsp70) member 6
MAPKAPK3 | mitogen-activated protein kinase-activated protein kinase 3

CA   SLC   SS

Signal transduction

**Color Key
and Histogran**

**ErbB signaling pathway
hsa04012**

AREG | amphiregulin
PRKCB | protein kinase C beta
MAPK3 | mitogen−activated protein kinase 3
STAT5A | signal transducer and activator of transcription 5A
SHC1 | SHC adaptor protein 1
TGFA | transforming growth factor alpha
PIK3CD | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit delta
GRB2 | growth factor receptor bound protein 2
PLCG2 | phospholipase C gamma 2
CAMK2G | calcium/calmodulin dependent protein kinase II gamma
PAK1 | p21 (RAC1) activated kinase 1
STAT5B | signal transducer and activator of transcription 5B
NRAS | NRAS proto−oncogene, GTPase
PIK3CB | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit beta
PIK3R5 | phosphoinositide−3−kinase regulatory subunit 5
CRK | CRK proto−oncogene, adaptor protein
GAB1 | GRB2 associated binding protein 1
SRC | SRC proto−oncogene, non−receptor tyrosine kinase
EGFR | epidermal growth factor receptor
PAK2 | p21 (RAC1) activated kinase 2
ARAF | A−Raf proto−oncogene, serine/threonine kinase
PIK3CG | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit gamma
CBL | Cbl proto−oncogene
MAPK1 | mitogen−activated protein kinase 1
SOS1 | SOS Ras/Rac guanine nucleotide exchange factor 1
BAD | BCL2 associated agonist of cell death
ABL2 | ABL proto−oncogene 2, non−receptor tyrosine kinase
NRG1 | neuregulin 1
PIK3CA | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit alpha
PAK3 | p21 (RAC1) activated kinase 3
GSK3B | glycogen synthase kinase 3 beta
SHC3 | SHC adaptor protein 3
NRG2 | neuregulin 2
MAP2K1 | mitogen−activated protein kinase kinase 1
MAP2K2 | mitogen−activated protein kinase kinase 2
EGF | epidermal growth factor
SHC2 | SHC adaptor protein 2
SHC4 | SHC adaptor protein 4
ERBB2 | erb−b2 receptor tyrosine kinase 2
PRKCG | protein kinase C gamma
KRAS | KRAS proto−oncogene, GTPase
RPS6KB2 | ribosomal protein S6 kinase B2
BRAF | B−Raf proto−oncogene, serine/threonine kinase
EREG | epiregulin
PIK3R2 | phosphoinositide−3−kinase regulatory subunit 2
BTC | betacellulin
EIF4EBP1 | eukaryotic translation initiation factor 4E binding protein 1

CA

SLC

SS

Signal transduction

**Color Key
and Histogran**

Count
0   30

−1.5   0   1
Value

Rap1 signaling pathway
hsa04015

RAC3 | Rac family small GTPase 2
ARHGAP26 | Rho GTPase-activating protein
ARHGAP3 | ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 3
RASGRP1 | Rap guanine nucleotide-releasing protein precursor protein 1 binding family B member 1 interacting protein
PGF | placental growth factor
PDGFRB | platelet-derived growth factor receptor subunit B
KDR | kinase insert domain receptor
PDGFC | platelet-derived growth factor C
VASP | vasodilator-stimulated phosphoprotein
MAPK3 | mitogen-activated protein kinase 3
GNB2 | G protein subunit beta 2 12
RAP1A | RAP1A, member of RAS oncogene family
RAPGEF5 | Rap guanine nucleotide exchange factor 5
PIK3CD | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
RALB | RAS like proto-oncogene B
RANBP9 | RAN binding protein 9
RAP2B | RAP2B, member of RAS oncogene family
RAP1B | RAP1B, member of RAS oncogene family
SIPA1 | signal-induced proliferation-associated 1
VEGFA | vascular endothelial growth factor A
F2RL3 | F2R like thrombin or trypsin receptor 3
ADORA2B | adenosine A2B receptor
F2R | coagulation factor II thrombin receptor
MRAS | muscle RAS oncogene homolog 11
RAP1GDS1 | Rap1 GTPase-GDP dissociation stimulator 1
RAPGEF3 | Rap guanine nucleotide exchange factor 3
PIK3CB | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta
DRD1 | dopamine receptor D1
EPHB2 | EPH receptor B2 encoding, receptor tyrosine kinase
CRKL | CRK like proto-oncogene, adaptor protein
MAP2K6 | mitogen-activated protein kinase kinase 6
PRKD2 | protein kinase D2
CSF1 | colony stimulating factor 1
SRC | SRC proto-oncogene, non-receptor tyrosine kinase
ADCY9 | adenylate cyclase 9
GNAO1 | G protein subunit alpha o1
RRAS | related RAS viral (r-ras) oncogene
RGS14 | regulator of G protein signaling 14
FLT1 | fms related receptor tyrosine kinase 1
PIK3CG | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma
RASGRP2 | RAS guanyl releasing protein 2
RAPGEF2 | Rap guanine nucleotide exchange factor 2
RAPGEF1 | Rap guanine nucleotide exchange factor 1
APBB1IP | amyloid beta precursor protein binding family B member 1 interacting protein
PLCE1 | phospholipase C epsilon 1
FYB1 | FYN binding protein 1 pleckstrin homology domain protein 2
FGFR3 | fibroblast growth factor receptor 3
KIT | KIT proto-oncogene, receptor tyrosine kinase
GNAI2 | G protein subunit alpha i2
PIK3CA | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
MAP2K1 | mitogen-activated protein kinase kinase 1
PRKCB | protein kinase C beta
GNAI3 | G protein subunit alpha i3
GRIN2A | glutamate ionotropic receptor NMDA type subunit 2A
MAP3K1 | mitogen-activated protein kinase kinase kinase 1
MAPK12 | mitogen-activated protein kinase 12
RGS14 | regulator of G protein signaling 14
ADCY7 | adenylate cyclase 7
PLCB1 | phospholipase C beta 1
ADRB1 | adrenoceptor beta 1
FGF11 | fibroblast growth factor 11
ADORA2A | adenosine A2A receptor
RAP2A | RAP2A, member of RAS oncogene GTPase
LPAR1 | lysophosphatidic acid receptor 1
FGF20 | fibroblast growth factor 20
FPR1 | formyl peptide receptor 1
LPAR2 | lysophosphatidic acid receptor 2
MAPK13 | mitogen-activated protein kinase 13
BRAF | B-Raf proto-oncogene, serine/threonine kinase
FGF5 | fibroblast growth factor 5
TIAM1 | T cell lymphoma invasion and metastasis 1
PIK3R2 | phosphoinositide-3-kinase regulatory subunit 2
RAC3 | Rac family small GTPase 3
VASP | vasodilator-stimulated phosphoprotein 1
CALML3 | calmodulin like 3

CA
SLC
SS

Signal transduction

**Color Key
and Histogran**

Count

0 15

−1   1

Value

HIF−1 signaling pathway
hsa04066

SERPINE1 | serpin family E member 1
EDN1 | endothelin 1
IL6R | interleukin 6 receptor
IFNGR1 | interferon gamma receptor 1
HKDC1 | hexokinase domain containing 1
FLT1 | fms related tyrosine kinase 1
PRKCB | protein kinase C beta
TIMP1 | TIMP metallopeptidase inhibitor 1
CYBB | cytochrome b−245 beta chain
MAPK3 | mitogen−activated protein kinase 3
ANGPT1 | angiopoietin 1
TFRC | transferrin receptor
PFKFB3 | 6−phosphofructo−2−kinase/fructose−2,6−biphosphatase 3
BCL2 | BCL2 apoptosis regulator
PIK3CD | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit delta
PLCG2 | phospholipase C gamma 2
HIF1A | hypoxia inducible factor 1 alpha subunit
CAMK2G | calcium/calmodulin dependent protein kinase II gamma
VEGFA | vascular endothelial growth factor A
NFKB1 | nuclear factor kappa B subunit 1
ANGPT2 | angiopoietin 2
PIK3CB | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit beta
SLC2A1 | solute carrier family 2 member 1
HK2 | hexokinase 2
PIK3R5 | phosphoinositide−3−kinase regulatory subunit 5
EGLN2 | egl−9 family hypoxia inducible factor 2
EGLN3 | egl−9 family hypoxia inducible factor 3
IFNGR2 | interferon gamma receptor 2
MKNK1 | MAP kinase interacting serine/threonine kinase 1
INSR | insulin receptor
RELA | RELA proto−oncogene, NF−kB subunit
EP300 | E1A binding protein p300
NOS2 | nitric oxide synthase 2
EIF4E2 | eukaryotic translation initiation factor 4E family member 2
EGFR | epidermal growth factor receptor
ARNT | aryl hydrocarbon receptor nuclear translocator
PIK3CG | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit gamma
LTBR | lymphotoxin beta receptor
MAPK1 | mitogen−activated protein kinase 1
STAT3 | signal transducer and activator of transcription 3
GAPDH | glyceraldehyde−3−phosphate dehydrogenase
EGLN1 | egl−9 family hypoxia inducible factor 1
HK3 | hexokinase 3
ENO1 | enolase 1
PIK3CA | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit alpha
ALDOA | aldolase, fructose−bisphosphate A
PGK1 | phosphoglycerate kinase 1
SERPINE1 | serpinE1 binding protein
NOX1 | NADPH oxidase 1
ANGPT4 | angiopoietin 4
MAP2K1 | mitogen−activated protein kinase kinase 1
MAP2K2 | mitogen−activated protein kinase kinase 2
VHL | von Hippel−Lindau tumor suppressor
EGF | epidermal growth factor
ERBB2 | erb−b2 receptor tyrosine kinase 2
PRKCG | protein kinase C gamma
LDHA | lactate dehydrogenase A
EPO | erythropoietin
NPPA | natriuretic peptide A
RPS6KB2 | ribosomal protein S6 kinase B2
NOX3 | NADPH oxidase 3
ELOC | elongin C
ELOB | elongin B
PIK3R2 | phosphoinositide−3−kinase regulatory subunit 2
PDHA1 | pyruvate dehydrogenase E1 alpha 1 subunit
PDHB | pyruvate dehydrogenase E1 beta subunit
EIF4EBP1 | eukaryotic translation initiation factor 4E binding protein 1
ENO3 | enolase 3

CA   SLC   SS

Signal transduction

**Color Key
and Histogran**

Count

0 15

−1   1

Value

FoxO signaling pathway
hsa04068

S1PB1 | sphingosine−1−phosphate receptor 1
TGFBR2 | transforming growth factor beta receptor 2
CCND2 | cyclin D2
KL | Klotho
CDKN2B | cyclin dependent kinase inhibitor 2B
RUFY1 | rubber like factor 2
MAPK3 | mitogen−activated protein kinase 3
TNFRSF10 | TNF receptor family member 10
S1PR4 | sphingosine−1−phosphate receptor 4
PIK3CD | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit delta
GRB2 | growth factor receptor bound protein 2
TGFB2 | transforming growth factor beta 2
CCNB2 | cyclin B2
PRKAA1 | protein kinase AMP−activated catalytic subunit alpha 1
SGK1 | serum/glucocorticoid regulated kinase 1
MAPK1 | mitogen−activated protein kinase 1
KRAS | KRAS proto−oncogene, GTPase
GABARAPL2 | GABA type A receptor−associated protein
CDKN2D | cyclin dependent kinase inhibitor 2D
PIK3CB | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit beta
PIK3R5 | phosphoinositide−3−kinase regulatory subunit 5
STK4 | serine/threonine kinase 4
TGFB3 | transforming growth factor beta 3
CCNB1 | cyclin B1
INSR | insulin receptor
TGFBR1 | transforming growth factor beta receptor 1
EP300 | E1A binding protein p300
PLK1 | polo like kinase 1
STK4 | serine/threonine kinase 4
CHUK | conserved helix−loop−helix ubiquitous kinase
G6PC3 | glucose−6−phosphatase catalytic subunit 3
EGFR | epidermal growth factor receptor
GABARAPL1 | GABA type A receptor associated protein like 2
BRAF | B−Raf proto−oncogene, serine/threonine kinase
PIK3CG | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit gamma
PTEN | phosphatase and tensin homolog
AGAP2 | ArfGAP with GTPase domain, ankyrin repeat and PH domain 2
FOXO1 | forkhead box O1
STAT3 | signal transducer and activator of transcription 3
FOXO3B | forkhead box O3B
RHOG | Ras homolog family member G
SOS1 | SOS Ras/Rac guanine nucleotide exchange factor 1
PIK3CA | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit alpha
MAPK14 | mitogen−activated protein kinase 14
SMAD4 | SMAD family member 4
MDM2 | MDM2 proto−oncogene
PDPK1 | 3−phosphoinositide dependent protein kinase 1
RBL2 | RB transcriptional corepressor like 2
CREBBP | CREB binding protein
MAP2K1 | mitogen−activated protein kinase kinase 1
MAPK12 | mitogen−activated protein kinase 12
EGF | epidermal growth factor
FOXO3 | forkhead box O3
USP7 | ubiquitin specific peptidase 7
BNIP3 | BCL2 interacting protein 3
PRKAG1 | protein kinase AMP−activated non−catalytic subunit gamma 1
PRKAB1 | protein kinase AMP−activated non−catalytic subunit beta 1
BRAF | B−Raf proto−oncogene
PRKAG2 | protein kinase AMP−activated non−catalytic subunit gamma 2
PRKAB2 | protein kinase AMP−activated non−catalytic subunit beta 2
GRM3 | glutamate metabotropic receptor 3
STK11 | serine/threonine kinase 11
MAPK13 | mitogen−activated protein kinase 13
BRAF | B−Raf proto−oncogene, serine/threonine kinase
IRS4 | insulin receptor substrate 4
FOXO3 | forkhead box O3
IRS2 | insulin receptor substrate 2
SGK2 | SGK2, serine/threonine kinase 2
PIK3R2 | phosphoinositide−3−kinase regulatory subunit 2
BNIP3 | BCL2 interacting protein 3

CA

SLC

SS

Signal transduction

**Color Key
and Histogram**

Count

0 80

−2   0   2

Value

PI3K−Akt signaling pathway
hsa04151

COL4A2 | collagen type IV alpha 2 chain

CA   SLC   SS

Signal transduction

**Color Key
and Histogram**

Count

**AMPK signaling pathway
hsa04152**

TBC1D1 | TBC1 domain family member 1
PPARG | peroxisome proliferator activated receptor gamma
PFKFB3 | 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3
CPT1A | carnitine palmitoyltransferase 1A
PIK3CD | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
PFKFB2 | 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2
PRKAA1 | protein kinase AMP-activated catalytic subunit alpha 1
PPP2R5B | protein phosphatase 2 regulatory subunit B beta
CAMKK2 | calcium/calmodulin dependent protein kinase kinase 2
PIK3CB | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta
PIK3R5 | phosphoinositide-3-kinase regulatory subunit 5
PPP2CB | protein phosphatase 2 catalytic subunit beta
CAB39 | calcium binding protein 39
CREB3 | cAMP responsive element binding protein 3
CRTC2 | CREB regulated transcription coactivator 2
INSR | insulin receptor
RAB14 | RAB14, member RAS oncogene family
CREB3L1 | cAMP responsive element binding protein 3 like 2
PPP2R5D | protein phosphatase 2 regulatory subunit B delta
CFTR | cystic fibrosis transmembrane conductance regulator
RHEB | Ras homolog, mTORC1 binding
RAB8A | RAB8A, member RAS oncogene family
G6PC | glucose-6-phosphatase catalytic subunit 3
PPP2R3C | protein phosphatase 2 regulatory subunit B''gamma
PIK3CG | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma
LIPE | lipase E, hormone sensitive type
GYS1 | glycogen synthase 1
FOXO3 | forkhead box O3
CAMKK1 | calcium/calmodulin dependent protein kinase kinase 1
PPP2CA | protein phosphatase 2 catalytic subunit alpha
HNF4A | hepatocyte nuclear factor 4 alpha
RAB1B | RAB1B, member RAS oncogene family
RAB2A | RAB2A, member RAS oncogene family
PIK3CA | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
CREB5 | cAMP responsive element binding protein 5
ACACB | acetyl-CoA carboxylase beta
PDPK1 | 3-phosphoinositide dependent protein kinase 1
ULK1 | unc-51 like autophagy activating kinase 1
STRADA | STE20-related kinase adaptor alpha
SCD5 | stearoyl-CoA desaturase 5
PPP2R2A | protein phosphatase 2 regulatory subunit Balpha
ACACA | acetyl-CoA carboxylase alpha
CPT1C | carnitine palmitoyltransferase 1C
AKT1S1 | AKT1 substrate 1
PFKM | phosphofructokinase, muscle
PRKAG1 | protein kinase AMP-activated non-catalytic subunit gamma 1
CCNA1 | cyclin A1
PRKAB1 | protein kinase AMP-activated non-catalytic subunit beta 1
PRKAG2 | protein kinase AMP-activated non-catalytic subunit gamma 2
RPS6KB2 | ribosomal protein S6 kinase B2
PRKAB2 | protein kinase AMP-activated non-catalytic subunit beta 2
ADRA1A | adrenoceptor alpha 1A
TSC1 | TSC complex subunit 1
STK11 | serine/threonine kinase 11
IRS4 | insulin receptor substrate 4
IRS2 | insulin receptor substrate 2
PFKFB4 | 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4
PIK3R2 | phosphoinositide-3-kinase regulatory subunit 2
RAB10 | RAB10, member RAS oncogene family
STRADB | STE20-related kinase adaptor beta
PPP2R2C | protein phosphatase 2 regulatory subunit Bgamma
MLYCD | malonyl-CoA decarboxylase
EIF4EBP1 | eukaryotic translation initiation factor 4E binding protein 1
GYS2 | glycogen synthase 2
SCD | stearoyl-CoA desaturase

CA

SLC

SS

Signal transduction

**Color Key
and Histogram**

Count

**VEGF signaling pathway
hsa04370**

−1.5 0 1
Value

RAC2 | Rac family small GTPase 2
KDR | kinase insert domain receptor
PRKCB | protein kinase C beta
PXN | paxillin
MAPK3 | mitogen−activated protein kinase 3
PLA2G4A | phospholipase A2 group IVA
PIK3CD | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit delta
PLCG2 | phospholipase C gamma 2
VEGFA | vascular endothelial growth factor A
MAPK11 | mitogen−activated protein kinase 11
NRAS | NRAS proto−oncogene, GTPase
PIK3CB | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit beta
PIK3R5 | phosphoinositide−3−kinase regulatory subunit 5
CDC42 | cell division cycle 42
SRC | SRC proto−oncogene, non−receptor tyrosine kinase
PPP3CA | protein phosphatase 3 catalytic subunit alpha
HSPB1 | heat shock protein family B (small) member 1
RAC1 | Rac family small GTPase 1
PIK3CG | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit gamma
MAPK1 | mitogen−activated protein kinase 1
MAPKAPK2 | mitogen−activated protein kinase−activated protein kinase 2
BAD | BCL2 associated agonist of cell death
PPP3R1 | protein phosphatase 3 regulatory subunit B, alpha
PIK3CA | phosphatidylinositol−4,5−bisphosphate 3−kinase catalytic subunit alpha
SPHK2 | sphingosine kinase 2
MAPK14 | mitogen−activated protein kinase 14
MAP2K1 | mitogen−activated protein kinase kinase 1
MAP2K2 | mitogen−activated protein kinase kinase 2
MAPK12 | mitogen−activated protein kinase 12
SHC2 | SHC adaptor protein 2
PRKCG | protein kinase C gamma
KRAS | KRAS proto−oncogene, GTPase
PPP3R2 | protein phosphatase 3 regulatory subunit B, beta
MAPK13 | mitogen−activated protein kinase 13
PIK3R2 | phosphoinositide−3−kinase regulatory subunit 2
SPHK1 | sphingosine kinase 1
RAC3 | Rac family small GTPase 3
MAPKAPK3 | mitogen−activated protein kinase−activated protein kinase 3

CA   SLC   SS

Signal transduction

**Color Key
and Histogran**

Count

−1 0 1

Value

Jak−STAT signaling pathway
hsa04630

IL2BG | interleukin 2 receptor subunit gamma
SPRY4 | sprouty RTK signaling antagonist 4
CCND2 | cyclin D2
IL6R | interleukin 6 receptor
IFNGR1 | interferon gamma receptor 1
IL4RI | interleukin 4 receptor
STAT5A | interleukin 15 receptor subunit alpha
STAT5A | signal transducer and activator of transcription 5A
OSMR | oncostatin M receptor
CCNDO | cyclin D3
IL6 | interleukin 6 family cytokine
JAK3 | Janus kinase 3
SOCS2 | suppressor of cytokine signaling 2
STAT1 | signal transducer and activator of transcription 1
PIK3CD | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
CSF2RA | colony stimulating factor 2 receptor alpha subunit
GRB2 | growth factor receptor bound protein 2
CSF2RB | colony stimulating factor 2 receptor beta common subunit
SOCN6 | suppressor of cytokine signaling 6
PTPN6 | protein tyrosine phosphatase non-receptor type 6
STAT5B | signal transducer and activator of transcription 5B
IL22RA1 | interleukin 22 receptor subunit alpha 1
JAK1 | Janus kinase 1
PIK3CB | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta
CCND1 | cyclin D1 receptor subunit beta
SPRED2 | sprouty related EVH1 domain containing 2
PIK3R5 | phosphoinositide-3-kinase regulatory subunit 5
IFNAR2 | interferon alpha and beta receptor subunit 2
SOCS5 | suppressor of cytokine signaling 5
IFNGR2 | interferon gamma receptor 2
JAK2 | Janus kinase 2
IL21 | interleukin 21
EP300 | E1A binding protein p300
TYK2 | tyrosine kinase 2
BCK2I | tyrosine kinase 2
PIK3CG | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma
CBL | Cbl proto-oncogene
PIAS4 | protein inhibitor of activated STAT 4
STAT3 | signal transducer and activator of transcription 3
IFNAR1 | interferon alpha and beta receptor subunit 1
SOS1 | SOS Ras/Rac guanine nucleotide exchange factor 1
PIAS1 | protein inhibitor of activated STAT 1
PIK3CA | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
CREBBP | CREB binding protein
CSF3R | colony stimulating factor 3 receptor
STAM | signal transducing adaptor molecule
CNTF | ciliary neurotrophic factor
IL9R | interleukin 9 receptor
CLRF2 | cytokine receptor like factor 2
IFNA1 | interleukin 3 receptor subunit alpha
IFNE | interferon epsilon
EPO | erythropoietin
IL20 | interleukin 20
IL22RA2 | interleukin 22 receptor subunit alpha 2
IFNL1 | interferon lambda 1
GH1 | growth hormone 1
IFNL2 | interferon lambda 2
IFNA5 | interferon alpha 5
IFNB1 | interleukin 11
SPRED3 | sprouty related EVH1 domain containing 3
IL21 | interleukin 21
IFNA21 | interferon alpha 21
IFNW1 | interferon omega 1
CSH2 | chorionic somatomammotropin hormone 2
IFNK | interferon kappa
IL20RB | interleukin 20 receptor subunit beta
EPOR | erythropoietin receptor
PIK3R2 | phosphoinositide-3-kinase regulatory subunit 2
IL13RA1 | interleukin 13 receptor subunit alpha 1
GHR | growth hormone receptor
PRLR | prolactin receptor

CA   SLC   SS

Signal transduction

Color Key and Histogram

Count
15
0

−3　0　2
Value

TNF signaling pathway hsa04668

TNFAIP3 | TNF alpha induced protein 3
CCL20 | C-C motif chemokine ligand 20
EDN1 | endothelin 1
JAG1 | jagged 1
CXCL1 | C-X-C motif chemokine ligand 1
ICAM1 | intercellular adhesion molecule 1
MMP9 | matrix metallopeptidase 9
TNFRSF1B | TNF receptor superfamily member 1B
NFKBIA | NFKB inhibitor alpha
VEGFC | vascular endothelial growth factor C
MAP3K8 | mitogen-activated protein kinase kinase kinase 8
CSF1 | colony stimulating factor 1
CEBPB | CCAAT/enhancer binding protein beta
MAPK3 | mitogen-activated protein kinase 3
VCAM1 | vascular cell adhesion molecule 1
IL6 | interleukin 6 family cytokine
PIK3CD | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
CASP10 | caspase 10
MLKL | mixed lineage kinase domain like pseudokinase
NFKB1 | nuclear factor kappa B subunit 1
CXCL3 | C-X-C motif chemokine ligand 3
MAPK11 | mitogen-activated protein kinase 11
MMP14 | matrix metallopeptidase 14
TNFRSF1A | TNF receptor superfamily member 1A
RIPK1 | receptor interacting serine/threonine kinase 1
FAS | Fas cell surface death receptor
CFLAR | CASP8 and FADD like apoptosis regulator
PIK3CB | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta
RIPK3 | receptor interacting serine/threonine kinase 3
PIK3R5 | phosphoinositide-3-kinase regulatory subunit 5
IL1B | interleukin 1 beta
ATF6B | activating transcription factor 6 beta
BCL3 | B-cell CLL/lymphoma 3
MAP2K6 | mitogen-activated protein kinase kinase 6
CREB3 | cAMP responsive element binding protein 3
IL18R1 | interleukin 18 receptor 1
MMP3 | matrix metallopeptidase 3
CASP8 | caspase 8
CREB3L2 | cAMP responsive element binding protein 3 like 2
RELA | RELA proto-oncogene, NF-kB subunit
PIK3CG | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma
CHUK | conserved helix-loop-helix ubiquitous kinase
IKBKG | inhibitor of nuclear factor kappa B kinase subunit gamma
MAPK1 | mitogen-activated protein kinase 1
FADD | Fas associated via death domain
DNM1L | dynamin 1 like
PIK3CA | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
CREB5 | cAMP responsive element binding protein 5
MAPK14 | mitogen-activated protein kinase 14
TNF | tumor necrosis factor
MAP2K1 | mitogen-activated protein kinase kinase 1
BAG4 | BCL2 associated athanogene 4
MAPK12 | mitogen-activated protein kinase 12
RPS6KA5 | ribosomal protein S6 kinase A5
MAP3K5 | mitogen-activated protein kinase kinase kinase 5
MAPK13 | mitogen-activated protein kinase 13
ITCH | itchy E3 ubiquitin protein ligase
NOD2 | nucleotide binding oligomerization domain containing 2
PGAM5 | PGAM family member 5, mitochondrial serine/threonine protein phosph..
PIK3R2 | phosphoinositide-3-kinase regulatory subunit 2
TAB3 | TGF-beta activated kinase 1 and MAP3K7 binding protein 3

CA　SLC　SS

Signal transduction

Color Key and Histogram

Count

0 15

−1 0 1

Value

Lysosome
hsa04142

CTSC | cathepsin C
LAPTM5 | lysosomal protein transmembrane 5
CTSK | cathepsin K
CTSZ | cathepsin Z
ASAH1 | N-acylsphingosine amidohydrolase
LAMP3 | lysosomal-associated membrane protein 3
LITAF | lipopolysaccharide induced TNF factor
CD63 | CD63 molecule
GNS | glucosamine (N-acetyl)-6-sulfatase
NPC2 | NPC intracellular cholesterol transporter 2
GM2A | GM2 ganglioside activator
RNASE2 | ribonuclease 2, lysosomal
CTSH | cathepsin H
PPT1 | palmitoyl-protein thioesterase 1
GLA | galactosidase alpha
TCIRG1 | T-cell immune regulator 1, ATPase H+ transporting V0 subunit a3
CTSO | cathepsin O
GAA | glucosidase alpha, acid
CTNS | cystinosin, lysosomal cystine transporter
IDS | iduronate 2-sulfatase
SLC17A5 | solute carrier family 17 member 5
AP1M1 | adaptor related protein complex 1 sigma 1 subunit
ASAH1 | N-acylsphingosine amidohydrolase 1
HEXB | hexosaminidase subunit beta
AP3M1 | adaptor related protein complex 1 mu 1 subunit
LAPTM4A | lysosomal protein transmembrane 4 alpha
MANBA | mannosidase beta
CD68 | CD68 molecule
IGF2R | insulin like growth factor 2 receptor
AP3M2 | adaptor related protein complex 1 mu 2 subunit
CLN3 | CLN3 lysosomal/intracellular trafficking protein
GALNS | galactosamine (N-acetyl)-6-sulfatase
ATP6V0A1 | ATPase H+ transporting V0 subunit a1
MCOLN1 | mucolipin 1
ATP6V0B | ATPase H+ transporting V0 subunit b
CLTB | clathrin light chain B
ARSA | arylsulfatase A
NEU1 | neuraminidase 1
GUSB | glucuronidase beta
CLTC | clathrin heavy chain
NAGA | alpha-N-acetylgalactosaminidase
AP4B1 | adaptor related protein complex 4 beta 1 subunit
CD164 | CD164 molecule
GALC | galactosylceramidase
AP4M1 | adaptor related protein complex 4 mu 1 subunit
SCARB2 | scavenger receptor class B member 2
ATP6V0D1 | ATPase H+ transporting V0 subunit d1
CTSD | cathepsin D
ABCA2 | ATP binding cassette subfamily A member 2
LAMP1 | lysosomal associated membrane protein 1
CTSA | cathepsin A
ATP6AP1 | ATPase H+ transporting accessory protein 1
GGA1 | golgi associated, gamma adaptin ear containing, ARF binding protein 1
NAPSA | napsin A aspartic peptidase
GNPTG | N-acetylglucosamine-1-phosphate transferase gamma subunit
GGA3 | golgi associated, gamma adaptin ear containing, ARF binding protein 3
ATP6V0C | ATPase H+ transporting V0 subunit c
AP1G1 | adaptor related protein complex 1 gamma 1 subunit
CTSF | cathepsin F
LAPTM4B | lysosomal protein transmembrane 4 beta
CTSA | cathepsin A
NAPSA | napsin A aspartic peptidase
AP3D1 | adaptor related protein complex 3 delta 1 subunit
AP3B1 | adaptor related protein complex 3 beta 1 subunit
CLTA | clathrin light chain A
AP1S1 | adaptor related protein complex 1 sigma 1 subunit
ATP6V1H | ATPase H+ transporting V1 subunit H
SUMF1 | sulfatase modifying factor 1
SGSH | N-sulfoglucosamine sulfohydrolase
ARSB | arylsulfatase B
AP3B2 | adaptor related protein complex 3 beta 2 subunit
CTSB | cathepsin B
ACP5 | acid phosphatase 5, tartrate resistant
ACP2 | acid phosphatase 2, lysosomal
RNASE6 | ribonuclease 2
ENTPD4 | ectonucleoside triphosphate diphosphohydrolase 4
AP1G2 | adaptor related protein complex 1 gamma 2 subunit
CLTCL1 | clathrin heavy chain like 1

CA SLC SS

Transport and catabolism

**Color Key
and Histogram**

Count

0   20

−1   1

Value

Phagosome
hsa04145

ITGA5 | integrin subunit alpha 5
HLA-B | major histocompatibility complex, class I, B
HLA-E | major histocompatibility complex, class I, E
COL EC12 | collectin subfamily member 12
CD1C | ATP binding cassette subfamily B member
MRC1 | mannose receptor C type 1
CYBB | cytochrome b-245 beta chain
C3 | complement C3
HLA-C | major histocompatibility complex, class I, C
TAP2 | transporter 2, ATP binding cassette subfamily B member
ITGB2 | complement C1r
TFRC | transferrin receptor
COL6 | collagen type VI
RAB5C | RAB5C, member RAS oncogene family
TUBA1B | tubulin alpha 1b
NCF4 | neutrophil cytosolic factor 4
NCF2 | neutrophil cytosolic factor 2
ITGAM | integrin subunit alpha M
MARCO | macrophage receptor with collagenous structure
CTSL | cathepsin L
ACTB | actin beta
TUBA4A | tubulin alpha 4a
RAB7A | RAB7A, member RAS oncogene family
ITGB5 | integrin subunit beta 5
VAMP3 | vesicle associated membrane protein 3
ATP6V0A3 | ATPase H+ transporting V0 subunit a3
ATP6V1C1 | ATPase H+ transporting V1 subunit C1
DYNC1LI2 | dynein cytoplasmic 1 light intermediate chain 2
RAB2A | RAB2A, member RAS oncogene family
SEC61A1 | Sec61 translocon alpha 1 subunit
CLEC7A | C-type lectin domain containing 7A
ITGB3 | integrin subunit beta 3
ATP6V1E1 | ATPase H+ transporting V1 subunit E1
SCARB1 | scavenger receptor class B member 1
DYNC1H1 | dynein cytoplasmic 1 heavy chain 1
MSR1 | macrophage scavenger receptor 1
THBS1 | thrombospondin 1
HLA-G | major histocompatibility complex, class I, G
ATP6AP1 | ATPase H+ transporting accessory protein 1
DYNC2H1 | dynein cytoplasmic 2 heavy chain 1
RAB7B | RAB7B, member RAS oncogene family
FCGR2A | Fc fragment of IgG receptor IIa
ATP6V0A1 | ATPase H+ transporting V0 subunit a1
ATP6V0B | ATPase H+ transporting V0 subunit b
THBS2 | thrombospondin 2
TLR6 | toll like receptor 6
OLR1 | oxidized low density lipoprotein receptor 1
ATP6V0B2 | ATPase H+ transporting V0 subunit B2
FCGR1B | Fc fragment of IgG receptor Ia
ATP6V0D1 | ATPase H+ transporting V0 subunit d1
RAB5A | Rab5 interacting lysosomal protein
LAMP2 | lysosomal associated membrane protein 2
CLEC6A | toll like receptor 6
ATP6AP2 | ATPase H+ transporting accessory protein 1
CANX | calnexin
ANXA2 | annexin A2
ATP6V0C | ATPase H+ transporting V0 subunit c
NSF | N-ethylmaleimide sensitive factor
SEC61A1 | Sec61 translocon alpha 1 subunit
STX7 | syntaxin 7
RAB5B | RAB5B, homolog B, vesicle trafficking protein (gene/pseudogene)
ATP6V1A | ATPase H+ transporting V1 subunit A
ITGB1 | integrin subunit beta 1
ATP6V1H | ATPase H+ transporting V1 subunit H
HGS | hepatocyte growth factor-regulated tyrosine kinase substrate
TUBAL3 | tubulin alpha like 3
TLR4 | toll like receptor 4
DYNC1LI1 | dynein cytoplasmic 1 light intermediate chain 1
FCGR2B | Fc fragment of IgG receptor IIb
RAB5B | RAB5B, member RAS oncogene family
TUBA1C | tubulin alpha 1c
NOX3 | NADPH oxidase 3
ATP6V1B1 | ATPase H+ transporting V1 subunit B1
SEC61A2 | Sec61 translocon alpha 2 subunit
ATP6V1C2 | ATPase H+ transporting V1 subunit C2
TUBB3 | tubulin beta 3 class III
ATP6V0E2 | ATPase H+ transporting V0 subunit e2

CA   SLC   SS

Transport and catabolism