Crucial Gene Identification in Carotid Atherosclerosis Based on Peripheral Blood Mononuclear Cell (PBMC) Data by Weighted (Gene) Correlation Network Analysis (WGCNA)

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Background: Many patients are not responsive or tolerant to medical therapies for carotid atherosclerosis. Thus, elucidating the molecular mechanism for the pathogenesis and progression of carotid atherosclerosis and identifying new potential molecular targets for medical therapies that can slow progression of carotid atherosclerosis and prevent ischemic events are quite important.

Material/Methods: We downloaded the expression profiling data of PBMC in Biobank of Karolinska Endarterectomy (BiKE, GSE21545) for GEO. The WGCNA and DEG screening were conducted. The co-expression pattern between patients with ischemic events (the events group) and patients without ischemic events (the no-events group) were compared. Then, we identified hub genes of each module. Finally, the DEG co-expression network was constructed and MCODE was used to identify crucial genes based on this co-expression network.

Results: In the study, 183 DEGs were screened and 8 and 6 modules were assessed in the events group and no-events group, respectively. Compared to the no-events group, genes associated with inflammation and immune response were clustered in the green-yellow module of the events group. The hub gene of the green-yellow module of the events group was KIR2DL5A. We obtained 1 DEG co-expression network, which has 16 nodes and 24 edges, and we detected 5 crucial genes: SIRT1, THRAP3, RBM43, PEX1, and KLHDC2. The upregulated genes (THRAP3 and RBM43) showed potential diagnostic and prognostic value for the occurrence of ischemic events.

Conclusions: We detected 8 modules for the events group and 6 modules for the no-events group. The hub genes for modules and crucial genes of the DEG co-expression network were also identified. These genes might serve as potential targets for medical therapies and biomarkers for diagnosis and prognosis. Further experimental and biological studies are needed to elucidate the role of these crucial genes in the progression of carotid atherosclerosis.

MeSH Keywords: Carotid Artery Diseases • Gene Expression Profiling • Gene Regulatory Networks • Microarray Analysis

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Background

Atherosclerosis is an inflammatory disease that involves the accumulation of fibrous and/or fatty components in the intima of medium and large arteries such as the coronary artery, carotid artery, and peripheral artery, and the clinical manifestations vary with the arteries affected [1, 2]. Ischemic strokes and transient ischemic attacks may occur if the carotid artery is involved, and carotid atherosclerotic disease accounts for approximately 18–25% of all ischemic strokes [3]. Prevention of stroke in patients with carotid atherosclerosis depends on the degree of carotid stenosis. These preventive methods mainly include carotid endarterectomy, carotid stenting, and medical management such as with statins and antiplatelet agents [4, 5]. Although the medical management is effective and may even serve as an alternative to carotid endarterectomy in patients with asymptomatic carotid atherosclerosis, patients who are nonresponsive to medical therapies or not tolerant of the adverse effects may not benefit from present medical therapies [6–8]. Therefore, elucidating the molecular mechanism of the pathogenesis and progression of carotid atherosclerosis and identifying new potential molecular targets for medical therapies that can slow progression of carotid atherosclerosis and prevent ischemic events are quite important. The molecular mechanism mainly includes abnormal accumulation of lipids, immune response, and inflammation, and monocytes play an important role [1, 9]. Induced by chemokines, circulating monocytes can bind to adhesion molecules expressed by endothelial cells, migrating into the arterial wall and differentiating into macrophages. Previous studies focused on the role of circulating monocytes in the pathogenesis and progression of carotid atherosclerosis; however, few researchers have used weighted (gene) correlation network analysis (WGCNA) to construct gene co-expression networks for carotid atherosclerosis based on high-throughput data of peripheral blood mononuclear cells (PBMCs) in patients.

Zhang and Horvath first developed the WGCNA algorithm in 2005, which can be used for gene co-expression network construction, gene module detection, and hub gene identification, based on gene expression data [10–12]. Furthermore, gene modules and hub genes can be correlated with clinical traits if these data are available. The WGCNA R package was developed on the official R website (https://cran.r-project.org/), making it more convenient for researchers to conduct WGCNA. Although WGCNA was first developed for analyzing gene expression data, it can also be used for miRNA, IncRNA, and even metabolome [13–15].

Previous studies screened differentially expressed genes (DEGs) using microarray data of carotid atherosclerotic plaques. For instance, Razuvaev et al. identified 11 downregulated genes and 19 upregulated genes by comparing the gene expression profile between symptomatic and asymptomatic patients [16]. However, DEG screening cannot reveal the interaction among genes or identify genes with crucial biological functions.

In the present study, we focused on the possible underlying molecular mechanism of the occurrence of ischemic events. The mRNA microarray data of the Biobank of Karolinska Endarterectomies (BiKE) were included. The expression data of peripheral blood mononuclear cells for patients with ischemic events (the events group) and patients without ischemic events (the no-events group) during follow-up [17] were used in our analysis. The genes in the gene modules were subjected to functional enrichment analysis. Then, we mapped DEGs into the co-expression network of events group and obtained 1 DEG co-expression network. Furthermore, we identified crucial genes based on the DEG co-expression network. The potential diagnostic and prognostics values of the upregulated crucial genes were identified.

Material and Methods

Datasets

The dataset GSE21545, from the Biobank of Karolinska Endarterectomies (BiKE), was selected from the Gene Expression Omnibus (GEO) (http://www.ncbi.nlm.nih.gov/geo/). Series matrix file and platform data tables (GPL570) were downloaded.

DEG analysis

The series matrix file was annotated with GPL570 platform data tables, and the probe names in the matrix file were replaced by the gene symbols. Then, the 97 peripheral blood mononuclear cell (PBMC) samples were included in our analysis, in which 21 were samples of the events group and 76 were samples of the no-events group. Differentially expressed genes (DEGs) were screened using the “limma” R package. \[|\log_{2}(\text{fold-change})|>2 \text{ and adjusted } p<0.01\] were set as the threshold of DEG screening.

Construction of co-expression network by WGCNA

Co-expression networks for both PBMC and plaque samples were constructed using the “WGCNA” R package. The algorithm filtered genes with the top 25% variance for further analysis, and WGCNA analysis was conducted for the events group (21 samples) and the no-events group (76 samples). The soft-power threshold \(b\) was chosen to ensure a scale-free topology. A topological overlap measure (TOM) matrix was created from the adjacency matrix to estimate the network’s connectivity property. A clustering dendrogram was constructed using average linkage hierarchical clustering based on the

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TOM matrix. The threshold for modules size was set as 50 for both groups to generate modules with proper size, and similar modules were merged.

**GO and KEGG pathway enrichment of gene modules**

Gene ontology (GO) and Kyoto Encyclopedia of Genes Genomes (KEGG) pathway analyses were conducted for genes in modules we detected using the Database for Annotation, Visualization and Integrated Discovery (DAVID) v6.8 (https://david.ncifcrf.gov/) to determine the biological function and signaling pathway involved in these modules. Count number >2 and p<0.05 were set as thresholds for the analysis. The differences between co-expression networks for the events group and no-events group were compared based on the results of functional enrichment analysis.

**Identification of hub genes and crucial genes**

Hub genes were considered to be the gene which had the largest intramodular connectivity in each module. Then, we mapped the DEGs into a co-expression network in the events group using Cytoscape v3.7.0, and we obtained 1 DEG co-expression network. Isolated nodes and isolated nodes pairs were removed from the network. The Molecular Complex Detection (MCODE), a plugin in Cytoscape to detect core subnetworks, was used to identify crucial gene clusters based on the DEG co-expression network. Receiver operating characteristic (ROC) analysis and survival analysis were also conducted using the combination of the upregulated genes in the crucial gene cluster by SPSS 25.0 to show the potential diagnostic and prognostic value of upregulated crucial genes.

**Results**

**Flowchart**

The flowchart of our study is shown in Figure 1. We constructed co-expression networks for the events group and no-events group and detected gene modules. Then, DEG screening was conducted, and 183 DEGs were screened. The DEG co-expression network was constructed by mapping DEGs into the whole co-expression network of the events group. Based on the DEG co-expression network, crucial genes were identified, and their clinical significance was evaluated by ROC and survival analysis.

**Screening of DEGs**

With the threshold of |log2(fold-change)|>2 and p<0.01, 183 DEGs were screened with 122 upregulated and 61 downregulated genes. The heatmap and the volcano plot showed the expression pattern of DEGs (Figure 2). Upregulated DEGs and downregulated DEGs with the top 10-fold-change are shown in Supplementary Table 1.

**Construction of the co-expression network for the events group and no-events group**

One outlier (GSM892524) in the events group was removed, while all samples in the no-events group were included for further analysis, as shown in the sample clustering dendrogram (Figure 3A and Supplementary Figure 1A). The power of β=10 and 16 were chosen as the soft-threshold for the network of the events group and no-events group, respectively (Figure 3B and Supplementary Figure 1B). And the both the co-expression networks we constructed met the requirements of scale-free topology (Figure 3C–3E and Supplementary Figure 1C–1E). We detected 8 gene modules for the events group and 6 gene modules for the no-events group (Figure 3F and Supplementary Figure 1F).

**Comparison of co-expression patterns**

KEGG pathway and GO-BP analysis were used to assess the biological function of genes for modules. Results of GO-BP and KEGG analyses are shown in Supplementary Tables 2 and 3. The green-yellow module may be related to the occurrence of ischemic events. The green-yellow module is mainly associated...
Figure 2. DEG screening. (A) Heatmap for the DEGs we screened. (B) Volcano plots for the DEGs. The X-axis represents –log(P.val) and Y-axis represents logFC.

Figure 3. WGCNA of event group. (A) One outlier (GSE89254) was detected by sample clustering. (B, C) Selection of soft-threshold β. (D, E) Fitness for scale free topology when β 10. (F) Cluster dendrogram. Each module was represented by WGCNA.
with inflammation and immune response. Nonetheless, pathways associated with inflammation and immune response were scattered in modules of the no-events group. The KEGG pathway GO-BP terms with the top 10 count numbers for green-yellow modules of the events group are shown in Figure 4 and Table 1. These results indicate that PBMC might play a role in the occurrence of ischemic events through regulating inflammation and immune response.

**Hub genes in modules of the events group and no-events group**

Hub genes for modules of the events group and no-events group are shown in Table 2. The hub genes of the green-yellow modules of the events group were killer cell immunoglobulin-like receptor, 2 Ig domains, and long cytoplasmic tail 5A (KIR2DL5A), which are killer cell immunoglobulin-like receptors (KIRs) and are mainly expressed by natural killer cells and subsets of T cells.

**Identification of crucial genes mediating ischemic events**

The DEG co-expression network was obtained by mapping DEGs into the whole co-expression network of the events group. The threshold for weighted edge was set as 0.1. After removing isolated nodes and isolated node pairs, a network with 16 nodes and 24 edges was generated (Figure 5A). MCODE detected 1 significant cluster consisting of 5 genes for the DEG co-expression network (Figure 5B, Table 3). Among these 5 genes, 2 genes were upregulated (THRAP3 and RBM43) and 3 genes were downregulated (SIRT1, PEX1, and KLHDC2). Sirtuin 1 (SIRT1), a member of the sirtuin family, had the highest connectivity among the 5 crucial genes.

Combination of the 2 upregulated genes showed potential diagnostic and prognostic value (Figure 6).
### Table 1. GO-BP KEGG pathways terms with top 10 count number of black module for events group.

| ID         | Terms                              | Count | -LogP |
|------------|------------------------------------|-------|-------|
| GO: 0006955 | Immune response                    | 24    | 11.80 |
| GO: 0007165 | Signal transduction                | 24    | 3.82  |
| GO: 0007166 | Regulation of immune response      | 18    | 12.65 |
| GO: 0007186 | G-protein coupled receptor signaling pathway | 15    | 1.63  |
| GO: 0006954 | Inflammatory response              | 14    | 4.60  |
| GO: 0007166 | Cell surface receptor signaling pathway | 13    | 5.34  |
| GO: 0045087 | Innate immune response             | 12    | 2.89  |
| GO: 0006915 | Apoptotic process                  | 12    | 1.99  |
| GO: 0006968 | Cellular defense response          | 9     | 7.24  |
| GO: 0008284 | Positive regulation of cell proliferation | 9     | 1.31  |

### KEGG

| ID         | Term                                | Count | -LogP |
|------------|-------------------------------------|-------|-------|
| hsa04650   | Natural killer cell mediated cytotoxicity | 19    | 14.53 |
| hsa04612   | Antigen processing and presentation | 15    | 12.70 |
| hsa04060   | Cytokine-cytokine receptor interaction | 11    | 3.16  |
| hsa04062   | Chemokine signaling pathway         | 7     | 1.59  |
| hsa05142   | Chagas disease (American trypanosomiasis) | 5     | 1.42  |
| hsa05332   | Graft-versus-host disease           | 4     | 2.13  |
| hsa05330   | Allograft rejection                 | 4     | 1.99  |
| hsa04940   | Type I diabetes mellitus            | 4     | 1.84  |
| hsa05321   | Inflammatory bowel disease (IBD)    | 4     | 1.37  |

### Table 2. Hub genes of each module for events group and no-events group.

| Module           | Gene symbol | Official full gene name                      |
|------------------|-------------|----------------------------------------------|
| **Events group** |             |                                              |
| Black            | ACRBP       | Acrosin binding protein                      |
| Blue             | AP2M1       | Adaptor related protein complex 2 subunit mu 1 |
| Green            | DOCK10      | Dedicator of cytokinesis 10                  |
| Magenta          | GNS         | Glucosamine (N-acetyl)-6-sulfatase           |
| Pink             | FHOD1       | Formin homology 2 domain containing 1        |
| Red              | ITGA5       | Integrin subunit alpha 5                    |
| Yellow           | MPEG1       | Macrophage expressed 1                      |
| **No-events group** |           |                                              |
| Black            | CTTN        | Cortactin                                    |
| Green            | PRKCSH      | Protein kinase C substrate 80K-H             |
| Magenta          | MAPRE1      | Microtubule associated protein RP/EB family member 1 |
| Red              | FAM103A1    | RNA Guanine-7 Methyltransferase Activating Subunit |
| Tan              | ZHX1        | Zinc fingers and homeoboxes 1               |
| Yellow           | ZBTB20      | Zinc finger and BTB domain containing 2      |
Discussion

We screened 183 DEGs, among which 122 were upregulated and 61 were downregulated. Weighted co-expression networks were constructed using the WGCNA algorithm. We detected 8 modules for the events group and 6 modules for the no-events group.

We also conducted KEGG pathway and GO-BP analysis (Supplementary Tables 2 and 3) and found that pathways related to inflammation and immune response were mainly enriched in the green-yellow module of the events group. However, these pathways were dispersed in modules of the no-events group.

Several previous studies conducted WGCNA on expression data of atherosclerosis. Using aortic samples from Apob<sup>−/−</sup>Ldlr<sup>−/−</sup> knockout mice, Deshpande et al. discovered that inflammation and immune response might play a role in the pathogenesis and progression of atherosclerosis, and identified several related genes (TM9SF1, LEPR, WIF1, and SP1). In contrast to the sample Desphande et al. used, some researchers used human atherosclerotic samples from the GEO website and also found that inflammation and immune response might have important roles. Zhang et al. discovered crucial genes such as TNPO1 and ZDHHC17, while Wang et al. found that a lncRNA module was associated with inflammation and immune response. However, they did not elucidate the molecular mechanism based on the expression profiling of PBMC samples, and the grouping was also different.

The gene module detection and functional enrichment analysis indicated that the co-expression patterns in the events group were distinct from those in the no-events group. Perisic et al. used the same dataset and analyzed the expression signature of PBMCs, and the DEGs they screened were different from the DEGs in our study. They grouped patients into a symptomatic group and an asymptomatic group. In the symptomatic group, patients already had plaque instability, which was defined as transient ischemic attack (TIA), minor stroke (MF), and amaurosis fugax (AF). However, unlike the previous study, we classified patients into an events group and a no-events group, depending on the occurrence of ischemic events during follow-up.

Table 3. Crucial genes detected by MCODE.

| Entrez ID | Gene symbol | Official full gene name          |
|----------|-------------|----------------------------------|
| 23411    | SIRT1       | Sirtuin 1                        |
| 9967     | THRAP3      | Thyroid Hormone Receptor Associated Protein 3 |
| 375287   | RBM43       | RNA Binding Motif Protein 43     |
| 23588    | KLHDC2      | Kelch Domain Containing 2        |
| 5189     | PEX1        | Peroxisomal Biogenesis Factor 1  |

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2 upregulated genes (THRAP3 and RBM43) showed potential prognostic and diagnostic value.

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In the symptomatic group, patients already had plaque instability, which was defined as transient ischemic attack (TIA), minor stroke (MF), and amaurosis fugax (AF). However, unlike the previous study, we classified patients into an events group and a no-events group, depending on the occurrence of ischemic events during follow-up. The difference in grouping patients may account for the difference in DEG screening results.

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our findings, suggest that monocytes participate in the pathogenesis and progression of atherosclerosis via mediating inflammation and immune response, both directly and indirectly.

The hub gene of the green-yellow module was KIR2DL5A, belonging to the KIR family, and it is mainly expressed by natural killer cells and T cells. KIR2DL5A is an inhibitory receptor of immune response [33] and it is involved in immune response to viral infection and prognosis of certain malignant diseases. Shan et al. reported that patients with KIR2DL5A+/2DL5B+ genotype had increased HCV clearance [34]. In colorectal cancer, the presence of KIR2DL5A is related to increased complete response rate in patients treated with FOLFIRI chemotherapy [35], and KIR2DL5A is also a protective factor against breast cancer [36], while in pediatric leukemia patients after hematopoietic stem cell transplantation, the presence of KIR2DL5A is associated with higher relapse rate [37]. However, few studies had reported the role of KIR2DL5A in monocytes or its role in atherosclerosis, and it might be a promising target to elucidate the molecular mechanism for the progression of carotid atherosclerosis.

SIRT1 was the gene having the highest degree among the 5 crucial genes, and it was downregulated in the events group. SIRT1 is a type of NAD-dependent histone deacetylase [38] and participates in regulating inflammation, apoptosis, and cell senescence [39,40]. It also plays roles in stress response, aging, and longevity [41,42]. SIRT1 can also slow the progression of atherosclerosis by lipid modification, oxidative stress reduction, anti-inflammatory actions, foam cells, and autophagy regulation, and downregulation of SIRT1 was observed in a atherosclerotic mouse model [43], which is consistent with
our findings. Recently, Lee et al. discovered that SIRT1 inhibits the adhesion of monocytes to vascular endothelial cells by suppressing MAC-1 expression in monocytes [44]. In addition, Nguyen et al. discovered that a dipeptidyl peptidase 4 inhibitor, evogliptin, can inhibit monocytes adhesion to vascular endothelial cells in an ApoE−/− mouse model, and this effect is associated with regulation of NF-κB by SIRT1 [45]. Therefore, SIRT1 might also slow the progression of atherosclerosis by preventing monocytes adhesion, which is one of the initiation steps in the pathogenesis of atherosclerosis.

The upregulated genes, THRAP3 and RBM43, showed potential diagnostic and prognostic value. THRAP3, thyroid hormone receptor-associated protein 3, is an RNA-processing factors and can also participate in the DNA damage response (DDR) pathway and transcription regulation [46–49]. Mutations in THRAP3 may cause DNA damage repair defects, and Vohhodina reported that loss of THRAP3 made 293T and U2OS cells more susceptible to DNA-damaging factors [49]. Ino et al. used LNCaP and LNCaP-AI prostate cancer cell lines to demonstrate that THRAP3 phosphorylation can contribute to the acquisition of androgen independence in prostate cancer via transcriptional regulation [48]. Another study, using high-fat-fed mice, found that THRAP3 can act as a transcriptional regulator in diabetes and can control diabetic gene programming [47]. RBM43 is an RNA binding motif protein 43 and its detailed biological function is not known. At present, it is unclear whether THRAP3 and RBM43 participates the pathogenesis of atherosclerosis, although they were found to have potential clinical significance for the occurrence of ischemic events in carotid atherosclerosis patients.

In the present study, for the first time, we constructed a co-expression network, detected genes modules, and identified hub genes and crucial genes in carotid atherosclerosis using PBMC expression data. However, datasets in GEO lack clinical information; therefore, it is difficult to correlate traits with clinical importance with gene modules in WGCNA analysis.

The events group and no-events group had different co-expression patterns, and these differences suggest that monocytes are of vital importance in the pathogenesis and progression of carotid atherosclerosis via mediating inflammation and immune response. Then, we identified hub genes and crucial genes, which might have crucial biological functions in the pathogenesis of carotid atherosclerosis or potential diagnostic and prognostic value for ischemic events.

**Conclusions**

We detected 8 modules for the events group and 6 modules for the no-events group. The hub genes for each module and crucial genes of the DEG co-expression network were also identified. These genes might serve as potential targets for medical therapies and as biomarkers for diagnosis and prognosis. Further mechanism studies are needed to explore the biological function of these genes in the pathogenesis and progression of carotid atherosclerosis.
Supplementary Figure 1. WGCNA of no-event. (A) No outlier was detected by sample clustering. (B, C) Selection of soft-threshold $\beta$. (D, E) Fitness of scale free topology when $\beta=16$. (F) Cluster dendrogram. Each module was represented by WGCNA.
**Supplementary Table 1.** Top10 up-regulated and down-regulated DEGs.

| Gene symbol | Official full gene name | log2 (fold-change) (patients with events/patients without events) |
|-------------|-------------------------|------------------------------------------------------------------|
| **Up-regulated** | | |
| TNFAIP6 | TNF alpha induced protein 6 | 9.968020902 |
| PTX3 | Pentraxin 3 | 8.826641354 |
| RNASE2 | Ribonuclease A family member 2 | 7.978917622 |
| KCNJ2 | Potassium inwardly rectifying channel subfamily J member 2 | 7.481378497 |
| SERPINB2 | Serpin family B member 2 | 7.18837765 |
| PLA2G7 | Phospholipase A2 group VII | 6.901998631 |
| BCL2A1 | BCL2 related protein A1 | 6.719719825 |
| CLEC4D | C-type lectin domain family 4 member D | 6.272368641 |
| SAMSN1 | SAM domain, SH3 domain and nuclear localization signals 1 | 6.209244405 |
| GPR84 | G protein-coupled receptor 84 | 5.186451434 |
| **Down-regulated** | | |
| KLRC3 | Killer cell lectin like receptor C3 | -7.246559422 |
| BTN3A2 | Butyrophilin subfamily 3 member A2 | -7.00383494 |
| ANKRD20A11P | Ankyrin repeat domain 20 family member A11, pseudogene | -6.02418399 |
| ZNF600 | Zinc finger protein 600 | -5.985685983 |
| NLR3C | NLR family CARD domain containing 3 | -5.579931019 |
| LCK | LCK proto-oncogene, Src family tyrosine kinase | -4.825468373 |
| GOLGA8N | Golgin A8 family member N | -4.799854266 |
| CEP78 | Centrosomal protein 78 | -4.795917474 |
| SLC9A3R1 | SLC9A3 regulator 1 | -4.381636674 |
| SEP1 | Septin 1 | -4.097540674 |

**Supplementary Table 2.** GO-BP terms for modules of events group and no events group.

Supplementary/raw data available from the corresponding author on request.
### DATABASE ANALYSIS

**Supplementary Table 3.** KEGG pathways for modules of events group and no-events group.

| Events group | KEGG ID | KEGG pathway               | Count | -logP | No-events group | KEGG ID | KEGG pathway               | Count | -logP |
|--------------|---------|----------------------------|-------|-------|-----------------|---------|----------------------------|-------|-------|
| Black        | hsa05034| Alcoholism                 | 14    | 4.58  | Black           | hsa04611| Platelet activation         | 11    | 5.10  |
|              | hsa05322| Systemic lupus erythematosus| 13    | 5.13  |                 | hsa05322| Systemic lupus erythematosus| 11    | 4.98  |
|              | hsa04611| Platelet activation        | 11    | 3.80  |                 | hsa05034| Alcoholism                  | 11    | 3.94  |
|              | hsa05203| Viral carcinogenesis       | 10    | 1.82  |                 | hsa04512| ECM-receptor interaction    | 8     | 3.83  |
|              | hsa05202| Transcriptional misregulation in cancer | 9     | 1.87  |                 | hsa05203| Viral carcinogenesis         | 8     | 1.71  |
|              | hsa04062| Chemokine signaling pathway| 9     | 1.62  |                 | hsa04510| Focal adhesion              | 8     | 1.70  |
|              | hsa04512| ECM-receptor interaction   | 6     | 1.62  |                 | hsa04810| Regulation of actin cytoskeleton | 8   | 1.66  |
|              | hsa04540| ECM-receptor interaction   | 6     | 1.62  |                 | hsa04530| Tight junction              | 5     | 1.54  |
|              | hsa04141| Prostatic processing of endoplasmic reticulum | 45   | 4.34  |                 | hsa05130| Pathogenic Escherichia coli infection | 4   | 1.52  |
|              | hsa05016| Huntington’s disease       | 38    | 1.42  |                 | hsa05930| Arachidonic acid metabolism | 5    | 1.32  |
|              | hsa04932| Non-alcoholic fatty liver disease (NAFLD) | 36    | 2.60  |                 | hsa04151| PI3K-Akt signaling pathway  | 16    | 1.30  |
|              | hsa05168| Herpes simplex infection  | 36    | 1.33  |                 | hsa04144| Endocytosis                 | 15    | 2.22  |
|              | hsa00190| Oxidative phosphorylation  | 31    | 2.13  |                 | hsa04141| Protein processing of endoplasmic reticulum | 13  | 2.66  |
|              | hsa04110| Cell cycle                 | 30    | 2.30  |                 | hsa05166| HTLV-I infection           | 5     | 1.54  |
|              | hsa04380| Osteoclast differentiation | 30    | 1.96  |                 | hsa04510| Focal adhesion             | 12    | 1.60  |
|              | hsa03040| Spliceosome                | 30    | 1.87  |                 | hsa04380| Osteoclast differentiation | 11    | 2.52  |
|              | hsa05132| Parkinson's disease        | 30    | 1.52  |                 | hsa04640| Neutrophilic cell lineage   | 2     | 2.61  |
|              | hsa05161| Hepatitis B                | 30    | 1.40  |                 | hsa04722| Neurotrophin signalling pathway | 9  | 1.78  |
|              | hsa04142| Lysosome                   | 27    | 1.65  |                 | hsa05220| Chronic myeloid leukemia    | 8     | 2.48  |
|              | hsa00240| Pyrimidine metabolism      | 25    | 2.09  |                 | hsa05230| Central carbon metabolism in cancer | 7 | 2.11  |
|              | hsa01200| Carbon metabolism          | 25    | 1.51  |                 | hsa05212| Pancreatic cancer           | 7     | 2.08  |
|              | hsa04660| T cell receptor signaling pathway | 23    | 1.58  |                 | hsa05100| Bacterial invasion of epithelial cells | 7 | 1.71  |
|              | hsa05132| Salmonella infection       | 22    | 2.21  |                 | hsa05132| Salmonella infection        | 7     | 1.59  |
|              | hsa05323| Rheumatoid arthritis       | 20    | 1.36  |                 | hsa04210| Apoptosis                   | 6     | 1.57  |
|              | hsa03018| RNA degradation            | 19    | 1.62  |                 | hsa04662| B cell receptor signaling pathway | 6 | 1.40  |
|              | hsa04210| Apoptosis                  | 18    | 2.26  |                 | hsa04962| Vasopressin-regulated water reabsorption | 5 | 1.50  |
|              | hsa05131| Shigellosis                | 18    | 2.11  |                 | hsa05010| N-Glycan biosynthesis       | 5     | 1.36  |
|              | hsa00510| N-Glycan biosynthesis      | 16    | 2.54  |                 |         | magenta                    |       |       |

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| Events group | KEGG ID   | KEGG pathway                          | Count | -logP | KEGG ID   | KEGG pathway                          | Count | -logP |
|--------------|-----------|---------------------------------------|-------|-------|-----------|---------------------------------------|-------|-------|
|              | hsa05221  | Acute myeloid leukemia                 | 15    | 1.60  | hsa04670  | Leukocyte transendothelial migration | 7     | 2.60  |
|              | hsa05134  | Legionellosis                          | 14    | 1.39  | hsa04142  | Lysosome                              | 7     | 2.48  |
|              | hsa00280  | Valine, leucine and isoleucine degradation | 13    | 1.50  | hsa04810  | Regulation of actin cytoskeleton       | 7     | 1.39  |
|              | hsa00520  | Amino sugar and nucleotide metabolism  | 13    | 1.43  | hsa04015  | Rap1 signaling pathway                | 7     | 1.39  |
|              | hsa05340  | Primary immunodeficiency               | 12    | 2.19  | hsa03008  | Ribosome biogenesis in eukaryotes     | 6     | 2.41  |
|              | hsa00710  | Fatty acyl-CoA oxidation                | 12    | 1.49  | hsa05331  | Shigellosis                           | 8     | 1.19  |
|              | hsa00640  | Propanoate metabolism                  | 10    | 1.86  | hsa04520  | Adherens junction                     | 5     | 1.98  |
|              | hsa03060  | Protein export                         | 9     | 1.92  | hsa05100  | Bacterial invasion of epithelial cells | 5     | 1.84  |
| Green        |           |                                       |       |       | hsa05132  | Salmonella infection                  | 5     | 1.75  |
|              | hsa03040  | Spliceosome                            | 8     | 2.34  | hsa03120  | Carbohydrate metabolism               | 5     | 1.37  |
|              | hsa05010  | Alzheimer’s disease                    | 8     | 1.81  | hsa05130  | Circadian rhythm                      | 4     | 2.22  |
|              | hsa04110  | Cell cycle                             | 6     | 1.36  | hsa04621  | NOD-like receptor signaling pathway   | 4     | 1.53  |
|              | hsa00310  | Lysine degradation                     | 5     | 2.07  | Red       | Pathogenic Escherichia coli infection | 4     | 1.63  |
|              | hsa04115  | p53 signaling pathway                  | 5     | 1.70  | hsa01100  | Metabolic pathways                   | 36    | 3.34  |
| Greenyellow  |           |                                       |       |       | hsa05010  | Alzheimer’s disease                   | 13    | 4.71  |
|              | hsa04650  | Natural killer cell mediated cytotoxicity | 19    | 14.53 | hsa05016  | Huntington’s disease                  | 13    | 4.14  |
|              | hsa04612  | Antigen processing and presentation    | 15    | 12.70 | hsa00190  | Oxidative phosphorylation            | 12    | 4.96  |
|              | hsa04060  | Cytokine-cytokine receptor interaction | 11    | 3.16  | hsa05012  | Parkinson’s disease                   | 12    | 4.69  |
|              | hsa04062  | Chemokine signaling pathway            | 7     | 1.59  | hsa04932  | Non-alcoholic fatty liver disease (NAFLD) | 9     | 2.46  |
|              | hsa05142  | Chagas disease (American trypanosomiasis) | 5     | 1.42  | hsa03010  | Ribosome                              | 8     | 2.14  |
|              | hsa05332  | Graft-versus-host disease              | 4     | 2.13  | hsa03050  | Proteasome                            | 4     | 1.44  |
|              | hsa05330  | Allograft rejection                    | 4     | 1.99  | hsa00520  | Amino sugar and nucleotide metabolism | 4     | 1.35  |
|              | hsa04940  | Type I diabetes mellitus               | 4     | 1.84  | Tan       | Allograft rejection                    | 4     | 1.99  |
|              | hsa05321  | Inflammatory bowel disease (IBD)       | 4     | 1.37  | hsa01100  | Metabolic pathways                   | 147   | 2.23  |
| Magenta      |           |                                       |       |       | hsa04120  | Ubiquitin mediated proteolysis        | 36    | 7.03  |
|              | hsa04010  | MAPK signaling pathway                 | 7     | 1.45  | hsa03013  | RNA transport                         | 33    | 3.48  |
|              | hsa04664  | Fc epsilon RI signaling pathway        | 4     | 1.55  | hsa04141  | Protein processing in endoplasmic reticulum | 30    | 2.64  |
| Pink         |           |                                       |       |       | hsa03040  | Spliceosome                           | 25    | 2.57  |
|              | hsa00516  | Herpes simplex infection               | 8     | 1.91  | hsa04110  | Herpes simplex infection             | 22    | 1.99  |
|              | hsa04931  | Insulin resistance                    | 6     | 1.80  | hsa03018  | RNA degradation                       | 21    | 4.38  |
|              | hsa04145  | Phagosome                              | 7     | 1.78  | hsa05161  | Hepatitis B                           | 21    | 1.09  |
|              | hsa04090  | Oxidative phosphorylation              | 6     | 1.86  | hsa04114  | Oxidative phosphorylation            | 11    | 1.17  |
| Red          |           |                                       |       |       | hsa03015  | mRNA surveillance pathway            | 17    | 1.78  |
| Events group | KEGG ID | KEGG pathway                        | Count | -logP | No-events group | KEGG ID | KEGG pathway                        | Count | -logP |
|--------------|---------|-------------------------------------|-------|-------|----------------|---------|-------------------------------------|-------|-------|
|              | hsa01100 | Metabolic pathways                  | 37    | 2.07  |                | hsa04070 | Phosphatidylinositol signaling system| 17    | 1.50  |
|              | hsa04114 | Oocyte meiosis                       | 8     | 2.17  | hsa04668       | TGF-β signaling pathway          | 17    | 1.20  |
|              | hsa04120 | Ubiquitin mediated proteolysis       | 8     | 1.70  |                | hsa04066 | HIF-1 signaling pathway            | 15    | 1.04  |
|              | hsa04668 | TNF signaling pathway                | 7     | 1.69  |                | hsa04720 | Long-term potentiation              | 14    | 1.93  |
|              | hsa04722 | Neurotrophin signaling pathway       | 7     | 1.48  |                | hsa05120 | Epithelial cell signaling in Helicobacter pylori infection | 13    | 1.51  |
|              | hsa04666 | Fc gamma R-mediated phagocytosis     | 6     | 1.58  |                | hsa04210 | Apoptosis                          | 12    | 1.40  |
|              | hsa05230 | Central carbon metabolism in cancer | 5     | 1.41  | hsa00562       | Inositol phosphate metabolism    | 12    | 1.04  |
|              | hsa05211 | Renal cell carcinoma                 | 5     | 1.37  |                | hsa00520 | Amino sugar and nucleotide sugar metabolism | 11    | 1.75  |
|              | hsa00010 | Glycolysis / Glucose metabolism      | 5     | 1.35  |                | hsa05130 | Pathogenic Escherichia coli infection | 11    | 1.58  |
|              | hsa04662 | B cell receptor signaling pathway    | 5     | 1.31  |                | hsa05110 | Vibrio cholerae infection           | 11    | 1.52  |
|              | hsa00512 | Mucin type O-Glycan biosynthesis     | 4     | 1.63  |                | hsa00510 | N-Glycan biosynthesis               | 10    | 1.30  |
|              | hsa00620 | Pyruvate metabolism                 | 4     | 1.34  |                | hsa00280 | Valine, leucine and isoleucine degradation | 9     | 1.05  |
| Yellow       | hsa05166 | Tuberculosis                         | 17    | 3.05  |                | hsa00320 | Nucleotide excision repair         | 1     | 9.05  |
|              | hsa04142 | Lysosome                            | 19    | 6.25  |                | hsa03060 | Protein export                      | 8     | 1.05  |
|              | hsa04145 | Phagosome                           | 19    | 4.88  |                | hsa03152 | N-Glycan biosynthesis               | 10    | 1.30  |
|              | hsa04164 | HLA class II                        | 17    | 1.00  |                | hsa03166 | HLA class II                       | 16    | 2.20  |
|              | hsa05166 | HTLV-I infection                    | 17    | 1.50  | hsa05152       | Tuberculosis                      | 11    | 2.00  |
|              | hsa04380 | Osteoclast differentiation           | 16    | 3.92  |                | hsa04010 | MAPK signaling pathway             | 11    | 1.08  |
|              | hsa05166 | Leishmaniasis                       | 13    | 4.92  |                | hsa04345 | Phagosome                          | 16    | 2.20  |
|              | hsa01130 | Biosynthesis of antibiotics          | 15    | 1.52  | hsa05168       | Herpes simplex infection         | 10    | 1.50  |
|              | hsa04640 | Hematopoietic cell lineage           | 14    | 4.68  |                | hsa05203 | Viral carcinogenesis                | 10    | 1.24  |
|              | hsa05140 | Leishmaniasis                       | 11    |       |                | hsa05161 | Hepatitis B                        | 9     | 1.64  |
|              | hsa05323 | Rheumatoid arthritis                | 13    | 3.96  | hsa05164       | Influenza A                       | 9     | 1.24  |
|              | hsa05145 | Toxoplasmosis                       | 12    | 2.54  |                | hsa05140 | Leishmaniasis                      | 8     | 2.83  |
|              | hsa04606 | NF-kappa B signaling pathway         | 11    | 2.80  | hsa04660       | T cell receptor signaling pathway | 8     | 2.00  |
|              | hsa05150 | Staphylococcus aureus infection      | 10    | 3.77  | hsa05169       | Epstein-Barr virus infection      | 8     | 1.57  |
|              | hsa04066 | Toll-like receptor signaling pathway | 10    | 1.72  | hsa04612       | Antigen processing and presentation | 7     | 2.02  |
|              | hsa04612 | Antigen processing and presentation | 9     | 2.11  | hsa05145       | Toxoplasmosis                     | 7     | 1.32  |
|              | hsa04666 | Fc gamma R-mediated phagocytosis     | 9     | 1.86  | hsa03040       | Spliceosome                       | 7     | 1.00  |
|              | hsa04660 | T cell receptor signaling pathway    | 9     | 1.45  | hsa05332       | Graft-versus-host disease         | 6     | 2.99  |
|              | hsa04672 | Intestinal immune network for IgA production | 8     | 2.75  | hsa05330       | Allograft rejection               | 6     | 2.76  |
| Events group | KEGG ID | KEGG pathway | Count | -logP | No-events group | KEGG ID | KEGG pathway | Count | -logP |
|--------------|---------|--------------|-------|-------|----------------|---------|--------------|-------|-------|
| Viral myocarditis | hsa05130 | Legionellosis | 8 | 2.40 | hsa04940 | Type I diabetes mellitus | 6 | 2.51 |
|  | hsa05321 | Inflammatory bowel disease (IBD) | 8 | 1.99 | hsa03050 | Proteasome | 6 | 2.42 |
|  | hsa01230 | Biosynthesis of amino acids | 8 | 1.73 | hsa05320 | Autoimmune thyroid disease | 6 | 2.11 |
|  | hsa05133 | Pertussis | 8 | 1.64 | hsa05416 | Viral myocarditis | 6 | 1.94 |
|  | hsa05204 | Chemical carcinogenesis | 8 | 1.50 | hsa05323 | Rheumatoid arthritis | 6 | 1.22 |
|  | hsa00480 | Glutathione metabolism | 7 | 1.92 | hsa05310 | Asthma | 5 | 2.27 |
|  | hsa05416 | Viral myocarditis | 7 | 1.69 | hsa04672 | Intestinal immune network for IgA production | 5 | 1.59 |
|  | hsa05310 | Asthma | 6 | 2.31 | hsa05223 | Non-small cell lung cancer | 5 | 1.35 |
|  | hsa05332 | Graft-versus-host disease | 5 | 1.46 | hsa05321 | Inflammatory bowel disease (IBD) | 5 | 1.17 |
|  | hsa00920 | Sulfur metabolism | 4 | 2.42 | hsa04662 | B cell receptor signaling pathway | 5 | 1.08 |
|  | hsa00511 | Other glycans degradation | 4 | 1.54 | hsa01230 | Biosynthesis of amino acids | 5 | 1.03 |
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**DATABASE ANALYSIS**

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