

# Comprehensive analysis of differentially expressed lncRNAs and associated ceRNA networks in Patau syndrome

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## Research

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# Abstract

**Objective:** LncRNAs are a class of competing for endogenous RNAs (ceRNAs) with no coding ability and have miRNA binding sites that competitively bind to miRNAs and inhibit miRNA-mediated regulation of target genes. In recent years, an increasing number of studies have recognized the biological functions of lncRNAs.

**Methods:** Illumina RNA-Seq technology was used to analyze the cord blood with Patau syndrome (PS) fetal and the peripheral blood of pregnant women to obtain differential expression profiles of lncRNAs, miRNAs, and mRNAs. Further, Combined with bioinformatics analysis of the biological functions of differentially expressed lncRNAs (DElncRNAs).

**Results:** The results showed that 467 DElncRNAs, 8512 differentially expressed mRNAs (DEmRNAs), and 18 differentially expressed miRNAs (DEmiRNAs) were found to be co-expressed in cord blood and peripheral blood. The hsa-miR-15a-5p is located on chromosome 13. We constructed the ceRNA network with hsa-miR-15a-5p, lncRNAs as the bait, and mRNAs as the target.

**Conclusion:** We consider that the DElncRNAs may indirectly regulate the target gene CLASRP or KARS by binding hsa-miR-15a-5p to participate in the occurrence of PS.

## Introduction

Patau Syndrome (PS) or trisomy 13, is a genetic disorder caused by a partial or complete trisomy of chromosome 13, with a prevalence of 1 in 4,000 live births[1]. Most children with PS die within a few hours or days after birth[2]. The clinical manifestations of PS include severe mental retardation, bradykinesia, difficulty speaking, etc. The complications of PS patients are congenital heart disease, urinary system malformation, polycystic hydronephrosis, etc[3]. The birth of children with PS has a huge economic burden on families and society. To reduce the birth of PS patients, prenatal intervention is mainly used to terminate the pregnancy of fetuses with PS. prenatal testing (NIPT) provides effective screening for PS[4]. The positive predictive values (PPVs) of NIPT for PS are 45%[5]. However, a baseline false-positive and false-negative rate remain in NIPT, so invasive prenatal screening is still important[6, 7]. The invasive prenatal screening will affect pregnant women and fetuses and may cause fetal miscarriage[8]. The occurrence of PS is related to maternal and aging ova[9]. At present, the pathogenesis of PS is unclear. Therefore, exploring the pathogenesis of PS is significant for mothers, families, and society.

Long non-coding RNA (lncRNA), with a length greater than 200 bp, is related to epigenetic regulation, cell cycle regulation, and cell differentiation regulation. Compared to coding RNAs, lncRNAs have fewer exons and lack an open reading frame (ORF) with a typical start codon and terminator. The function of most lncRNAs remains undiscovered[10]. Recently, more and more studies have found that lncRNA is closely related to human diseases. It was confirmed by RNA sequencing that the qRT-PCR data lncRNA growth arrest-specific 5(GAS5) was down-expressed in DS patients, which may be related to some characteristics

of DS patients[11]. Compared with normal-iPSCs, differentially expressed lncRNAs (DElncRNAs) closely related to mitochondrial function were found in Down syndrome induced pluripotent stem cells (DS-iPSCs). Down syndrome-iPSCs, and almost all genes related to mitochondria were down-regulated[12]. Other research showed that the study of the CNIB1 lncRNAs on zebrafish provides a lncRNA cluster-mediated pathophysiological mechanism for human Chr9q33.3-9q34.11 microdeletion syndrome[13].

The rapid development of high-throughput sequencing technology has greatly promoted transcriptome sequencing (RNA-Seq). RNA-Seq is widely used in various researches. To explore the pathogenesis of PS, we constructed the RNA library and analyzed the expression profiles of lncRNAs, miRNAs, and mRNAs in the cord blood of fetuses with PS and the peripheral blood of pregnant women. Subsequently, lncRNAs were analyzed in conjunction with GO and KEGG pathway databases. Our research reveals the ceRNA regulatory network that may be involved in the occurrence and development of PS and provides new ideas for the pathogenesis of PS.

## Materials And Methods

### Human samples

Informed consent was obtained from the participants (aged 30–40 years), including pregnant women with a PS fetus and pregnant women with a healthy fetus. From July 2016 to July 2017, the peripheral blood (PS2) and umbilical cord blood (PS1) of pregnant women with a PS fetus was collected at Shenzhen People's Hospital as the disease group. Two pregnant women with healthy fetuses served as healthy controls. One of the pregnant women received peripheral blood (NC2) and the other pregnant woman received umbilical cord blood (NC1). We have compiled information on disease groups and healthy controls (Table 1). The fetus is diagnosed as a patient with PS by chromosome G banding.

Table 1  
Information on the sample

Age	Sample type	Clinical diagnosis	Karyotype	Number
36	Cord blood	patau syndrome	47,XX,+13	PS -1
36	Peripheral blood	patau syndrome	46,XX	PS-2
40	Cord blood	normal	46,XY	NC-1
32	Peripheral blood	normal	46,XX	NC-2

## RNA extraction

Extract RNA from peripheral blood and cord blood. The purity and concentration of RNA were evaluated with NanoDrop ND-1000 (Thermo Fisher Scientific, Wilmington, DE). RNA integrity was assessed using the RNA Nano 6000 Assay Kit of the Bioanalyzer 2100 system (Agilent Technologies, CA, USA)

## Library preparation for RNA sequencing

A total of 3 µg RNA per sample was used as the starting amount for RNA library preparation. Sequencing libraries were generated using the rRNA-depleted and RNase R-digested RNA samples by NEBNext® Ultra Directional RNA Library Prep Kit for Illumina® (NEB, USA) following the manufacturer's recommendations. The libraries were purified by the AMPure XP system and then analyzed by the Agilent Bioanalyzer 2100 system.

## Clustering and sequencing

The clustering of the index-coded samples was performed on a cBot Cluster Generation System using a HiSeq PE Cluster Kit v3 cBot (Illumina) according to the manufacturer's instructions. After cluster generation, the library preparations were sequenced on an Illumina HiSeq 2500 platform, and 50/125 bp paired-end reads were generated. Differential expression analysis of lncRNAs was performed using DESeq software. The screening conditions of mRNA, lncRNA, and miRNA were (1)  $|\log_2(\text{fold change})| \geq 1$ ; (2)  $P < 0.05$ .

## GO and KEGG enrichment analyses

To understand the potential biological functions and pathways of candidate target genes in the ceRNA regulatory network, we performed Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) functional enrichment analysis on differentially expressed RNAs. Significance was inferred when  $P < 0.05$ .

# Results

## Expression profiles of lncRNAs

To study the potential functions of lncRNAs in PS, we obtained differential expression profiles of lncRNAs from cord blood and peripheral blood. We identified (DElncRNAs) based on  $|\log_2(\text{fold change})| > 1$  and  $P$  value  $< 0.05$ . Compared with normal controls, 1146 DElncRNAs were screened from cord blood, of which 752 DElncRNAs were down-regulated and 394 DElncRNAs were up-regulated. 1226 DElncRNAs were screened from the peripheral blood of pregnant women, of which 626 DElncRNAs were down-regulated and 600 was up-regulated. DElncRNAs are displayed with a volcano map (Fig. 1). Cord blood and peripheral blood co-express 467 DElncRNAs, which is shown by the Venn diagram (Fig. 2).

## Expression profiles of miRNAs

We identified differentially expressed miRNAs (DEmiRNAs) based on  $|\log_2(\text{fold change})| > 1$  and  $P$ -value  $< 0.05$ . A total of 147 differentially expressed miRNAs were screened from cord blood, of which 94 DEmiRNAs were down-regulated and 53 DEmiRNAs were up-regulated. A total of 45 differentially expressed miRNAs were screened from the peripheral blood of pregnant women, of which 27 DEmiRNAs were down-regulated and 18 DEmiRNAs were up-regulated. DEmiRNAs are displayed with a volcano map

(Fig. 1). Cord blood and peripheral blood co-express 18 DE miRNAs, which are shown by the Venn diagram (Fig. 2).

### Expression profiles of mRNAs

We identified differentially expressed mRNAs (DE mRNAs) based on  $|\log_2(\text{fold change})| > 1$  and  $P\text{-value} < 0.05$ . A total of 17762 DE mRNAs were screened from cord blood, of which 6558 DE mRNAs were up-regulated and 11204 DE mRNAs were down-regulated. A total of 20932 DE mRNAs were screened from the peripheral blood of pregnant women, of which 8317 DE mRNAs were down-regulated and 12615 DE mRNAs were up-regulated. DE mRNAs are displayed with a volcano map (Fig. 1). Cord blood and peripheral blood co-express 8512 DE mRNAs, shown by the Venn diagram (Fig. 2).

### Enrichment analysis of DE lncRNAs

GO analysis was performed on the differentially expressed lncRNA-targeted mRNAs in cord blood and peripheral blood, including co-located and co-expressed mRNAs. In cord blood, the lncRNAs-targeted mRNAs (co-expressed) were associated with 12571 BPs such as metabolic process and organic substance metabolic process, 3950 MFs such as binding and protein binding, and 1551 CCs such as cell and cell part (Fig. 3A). Also, the lncRNAs-targeted mRNAs (co-located) were associated with 8176 BPs (biological processes) such as metabolic process and organic substance metabolic process, 1934 MFs (molecular functions) such as binding and ion binding, and 1008 CCs (cellular components) such as intracellular and intracellular part (Fig. 2B). In peripheral blood, the lncRNAs-targeted mRNAs (co-expressed) were associated with 12569 BPs such as metabolic process and organic substance metabolic process, 3947 MFs such as binding and protein binding, and 1544 CCs such as cell and cell part (Fig. 2C). Also, the lncRNAs-targeted mRNAs (co-located) were associated with 8323 BPs such as metabolic process and organic substance metabolic process, 2034 MFs such as binding and protein binding, and 1019 CCs such as intracellular membrane-bounded organelle and (Fig. 2D).

KEGG was performed on the differentially expressed lncRNA-targeted mRNAs. In cord blood, the DE lncRNA targeted mRNAs (co-located mRNAs) were related to pathways such as the ubiquinone and other terpenoid – quinone biosynthesis, and homologous recombination (Fig. 3A). Also, the DE lncRNA targeted mRNAs (co-expressed mRNAs) were related to pathways such as the Base excision repair and colorectal cancer (Fig. 3B). In peripheral blood, the DE lncRNA targeted mRNAs (co-located mRNAs) were related to pathways such as ascorbate and aldarate metabolism, and pentose and glucuronate interconversions (Fig. 3C). Also, the DE lncRNA targeted mRNAs (co-expressed mRNAs) were related to pathways such as DNA replication and Fc gamma R – mediated phagocytosis (Fig. 3D).

### Analysis of the ceRNA network of lncRNAs, miRNAs, and mRNAs

Hierarchical clustering revealed 18 DE miRNAs co-expressed in cord blood and peripheral blood (Fig. 4A). Searching the database miRBase found that hsa-miR-15a-5p is located on chromosome 13 (chr13:50049167–50049188). In cord blood, hsa-miR-15a-5p is down-regulated (-1.7221-fold change); In

peripheral blood, hsa-miR-15a-5p is up-regulated ( 1.1011-foldchange). Therefore, with hsa-miR-15a-5p as the center, lncRNAs as the bait, and mRNAs as the target, we constructed the network of lncRNAs-miRNAs-mRNAs. In cord blood, we constructed a network of lncRNAs-miRNAs-mRNAs with a total of 163 lncRNAs, 1 miRNA (hsa-miR-15a-5p), and 2 mRNAs (Fig. 4B). Also, in peripheral blood the lncRNAs-miRNAs-mRNAs network with a total of 157 lncRNAs, 1 miRNA (hsa-miR-15a-5p), and 3 mRNAs (Fig. 4C). Moreover, the ceRNA of cord blood, two DEmRNAs (KARS and CLASRP) combined with hsa-miR-15a-5p. Both KARS (-4.4896-foldchange) and CLASRP (-6.59434-foldchange) were down-regulated. The ceRNA of peripheral blood, three DEmRNAs (SELENOO, KARS, and CLASRP) bind to hsa-miR-15a-5p. KARS (9.1837-foldchange) and CLASRP (3.1769-foldchange) are both up-regulated, SELENOO (-2.1339-foldchange) is down-regulated. A total of 59 DElncRNAs are combined with hsa-miR-15a-5p in cord blood and peripheral blood. Further, DElncRNAs were found to share a common binding site of miRNA, and DElncRNAs target a common mRNA. For example, LNC-000011, LNC-000710, and LNC-000747 are ceRNA of hsa-miR-15a-5p targeting CLASRP, KARS, and SELENOO.

## Discussion

PS is a chromosomal disorder caused by an abnormal number of chromosome 13. The clinical manifestations of PS are diverse, such as mental retardation, microphthalmia, upper cleft lip, which are often accompanied by other conditions. the complications of PS including congenital heart disease, hydronephrosis, polycystic kidney, etc. At present, there is no effective way to treat PS. The birth of a child with PS brings great mental stress and financial burden to the family and society. With the wide application of RNA-seq technology, non-coding RNA (such as miRNA, lncRNA, and circRNA) is associated with many diseases, including Down syndrome[11–12]. In our research, we use RNA-seq analysis to detect non-coding RNA (lncRNA, mRNA, and miRNA) and obtain its differential expression profile. A total of 1146 DElncRNAs, 17762 DEmRNAs, and 147 DEmiRNAs are differentially expressed in cord blood and a total of 1226 DElncRNAs, 20932 DEmRNAs, and 45 DEmiRNAs are differentially expressed in peripheral blood.

lncRNA is defined as an RNA molecule that is more than 200 nucleotides in length but has no protein-coding ability. Compared with mRNA, lncRNA does not have a coding function, its expression level is low, and it is mainly enriched in the nucleus.

lncRNA directly binds to mRNA to regulate its expression and translation[14]; lncRNA can also act as a target decoy for miRNA, promote/inhibit miRNA expression, thereby affecting gene expression. For example, lncRNA TUC338 promotes the invasion and migration of bladder cancer cells by upregulating miR-10b[15]. The upregulation of the LINK-A lncRNA may serve as a potential diagnostic biomarker for patients with MO. LINK-A lncRNA participates in the metastasis of osteosarcoma by upregulating HIF1 $\alpha$ [16]. Wang reported that the silencing of noncoding RNA MALAT 1 inhibits the proliferation, migration, and invasion of esophageal squamous cell carcinoma cells via miR-101 and miR-217[17].

GO and KEGG enrichment analyses were performed on DElncRNAs targeted genes. The GO analysis consists of three domains, which are called cellular components, biological processes, and molecular functions. GO enrichment analysis shows that DElncRNAs targeted co-located mRNAs and DElncRNAs targeted co-expressed mRNAs are mainly involved in protein binding, cell composition, and biological metabolism. KEGG pathway enrichment analysis shows that DElncRNAs co-located mRNAs and co-expressed mRNAs are mainly involved in the metabolic process, it is possible to participate in the occurrence and development of PS.

The pathogenesis of PS is not yet clear. This article studies the DElncRNAs in cord blood of PS fetal and normal control cord blood, as well as the peripheral blood of pregnant women with PS and pregnant women with normal fetuses. Based on the principle of ceRNA, we construct a visual regulatory network centered on DEmiRNA. We found that there are 18 DEmiRNAs in peripheral blood and umbilical cord blood, of which hsa\_miRNA\_15a\_5p is located on chromosome 13. We use hsa\_miRNA\_15a\_5p as the central node to construct a ceRNA regulatory network. Nervous system diseases are associated with dysregulation of miRNA. The overexpression of miR-15a-5p is associated with the vitality of hippocampal neurons in children with Temporal lobe epilepsy (TLE) and is a potential biomarker for the diagnosis of TLE in children. Therefore, the differential expression of hsa\_miRNA\_15a\_5p may be related to PS mental retardation[18]. 59 DElncRNAs are combined with hsa-miR-15a-5p targeting CLASRP or KARS. Salemi et al [11] found that compared with normal controls, LncRNA GAS5 was down-expressed in 23 patients with DS, which may be related to some typical clinical features of DS patients. Also, DElncRNAs may cause mitochondrial dysfunction in Down syndrome[19]. Therefore, in this study, the 59 DElncRNAs may be combining with hsa\_miRNA\_15\_5p indirectly regulate the target genes ( CLASRP or KARS), and participate in the occurrence of PS.

## Conclusion

Through sequencing and bioinformatics analysis of the cord blood of PS and peripheral blood of pregnant women, we constructed the expression profile of DElncRNAs, DEmRNAs and DEmiRNAs. 59 DElncRNAs may indirectly regulate the target gene CLASRP or KARS by binding hsa-miR-15a-5p to participate in the occurrence of PS.

## Declarations

### Acknowledgments

We thank all patients who took part in this study.

### Author Contributions

DT and YD contributed to the conceptualization; JC, YD, and DT contributed to the methodology; JC, JZ, ZH and HH contributed to the data curation; JC and DT contributed to the writing of the original draft and preparation; JC, HL, and WS contributed to the writing like review and editing; YD is responsible for the

supervision; DT and YD contributed to the project administration; DT and YD contributed to the funding acquisition. All authors read and approved the final manuscript.

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## **Statement of Ethics**

All experimental protocols of this study were approved by the Shenzhen People's Hospital. All methods were carried out following relevant guidelines and regulations. This study was approved by the Ethics Committee of Shenzhen People's Hospital, which abided by the ethical principles of the Helsinki Declaration of 1975 (revised in 2000).

## **Conflict of Interest**

The authors declare that they have no conflict of interest.

## **Availability of data and materials**

The data are available from the corresponding author on reasonable request.

## **Consent for publication**

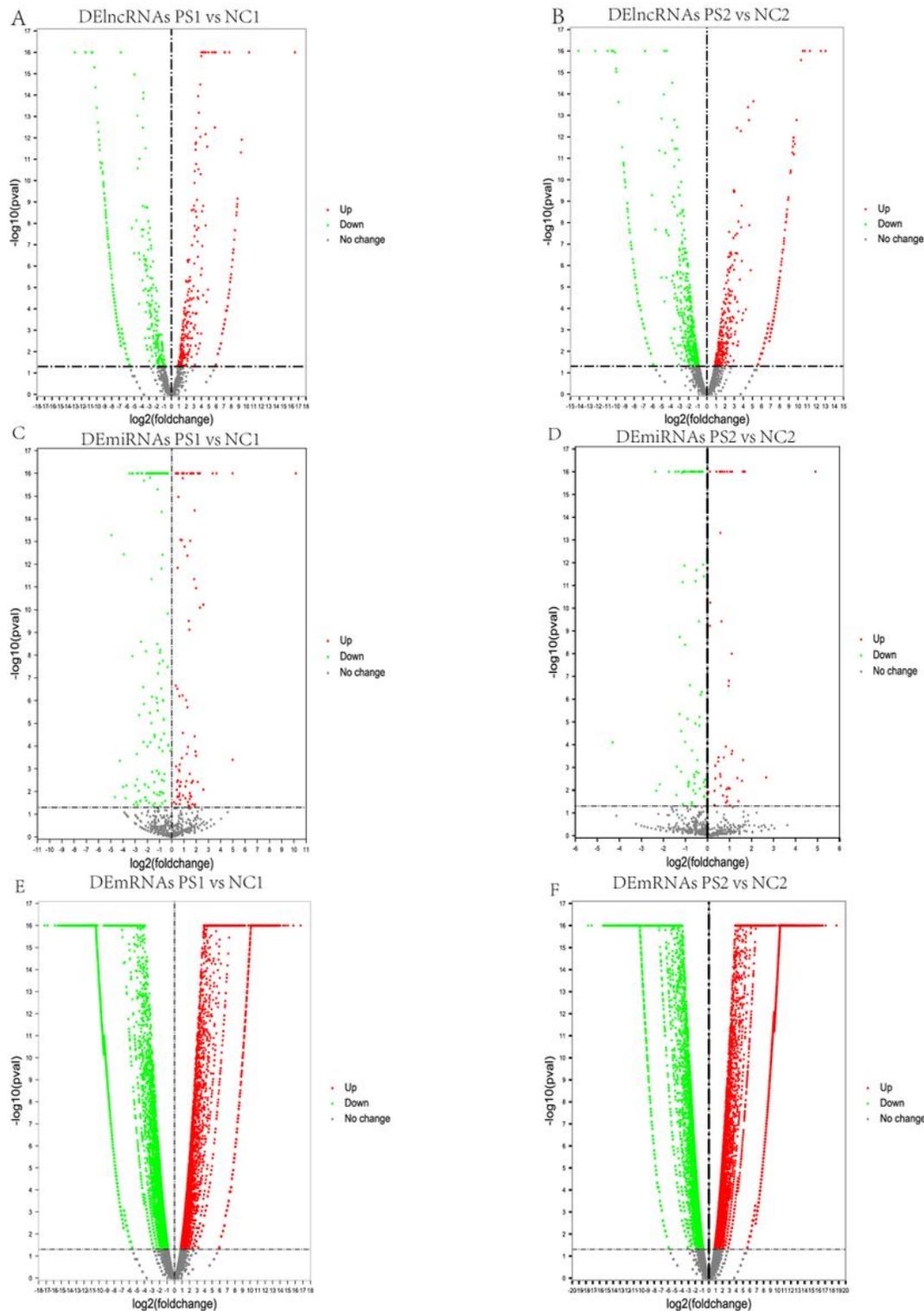
Informed consent was obtained from all participants

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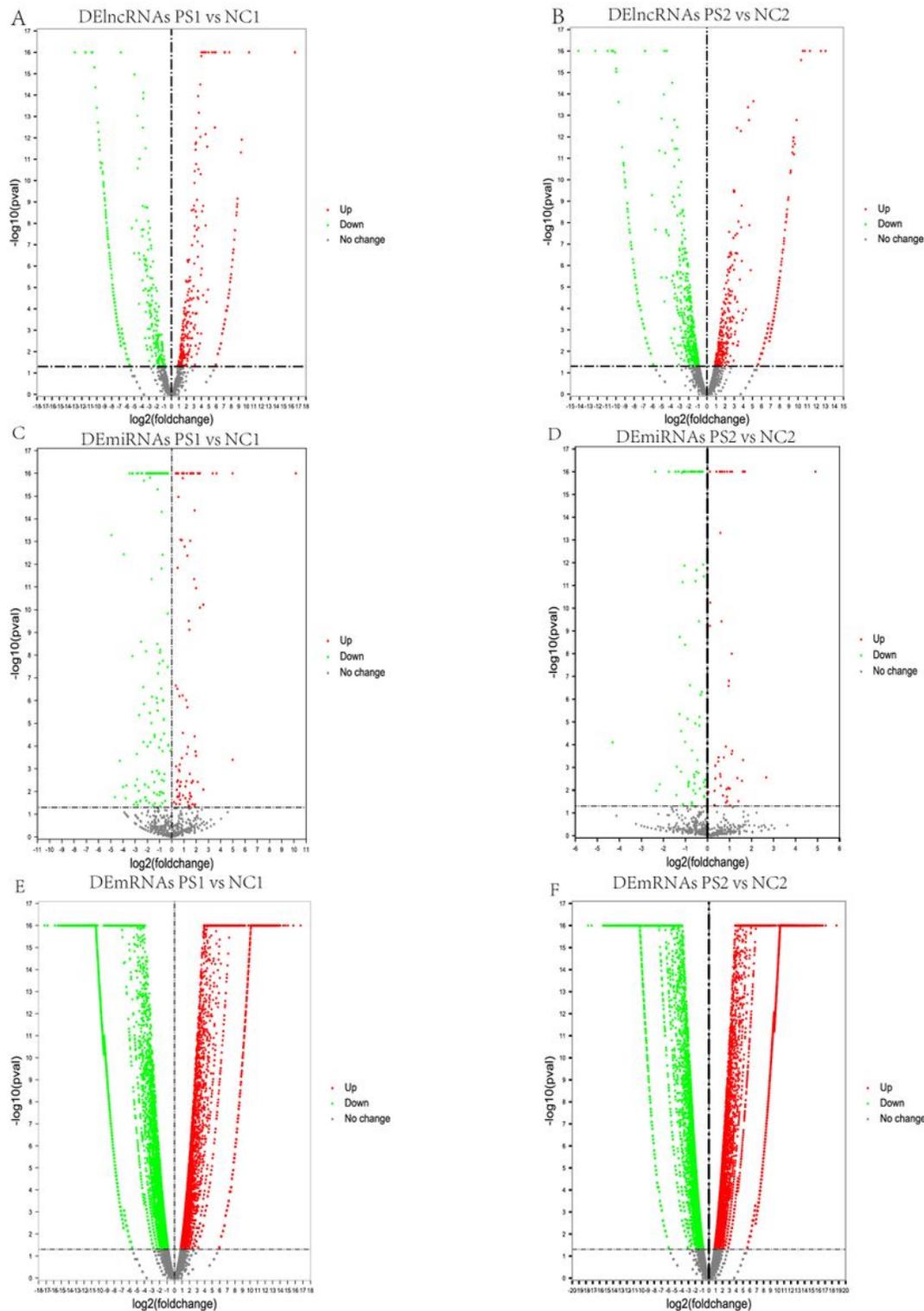
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## Figures



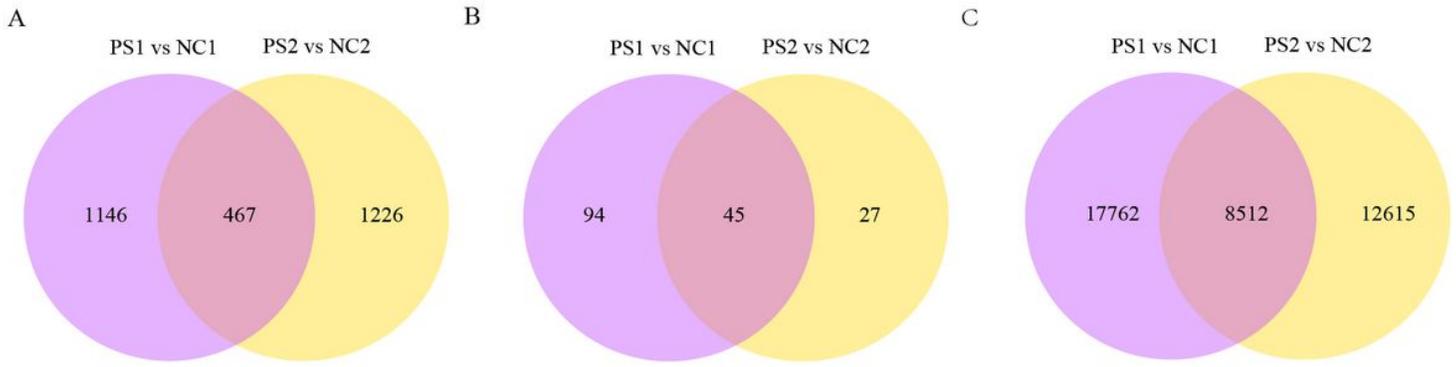
**Figure 1**

Differential expression of nRNAs. Volcanic map of DEIncRNAs (A), DEmiRNAs (C), and DEmRNAs (E) in cord blood. Volcanic map of DEIncRNAs (B), DEmiRNAs (D), and DEmRNAs (F) in peripheral blood. Red dots represent upregulated nRNAs, green dots represent downregulated nRNAs, and without significant differential expression is represented by gray.



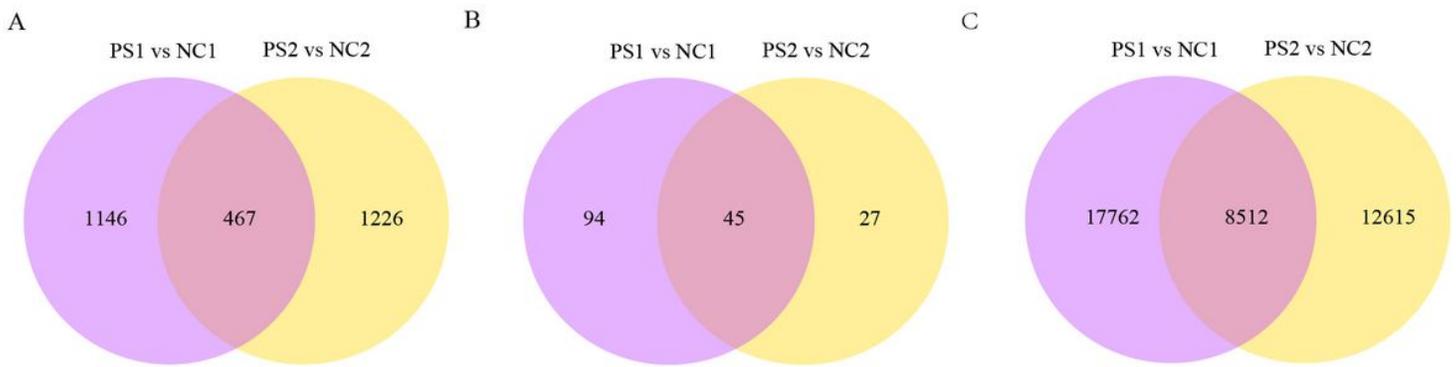
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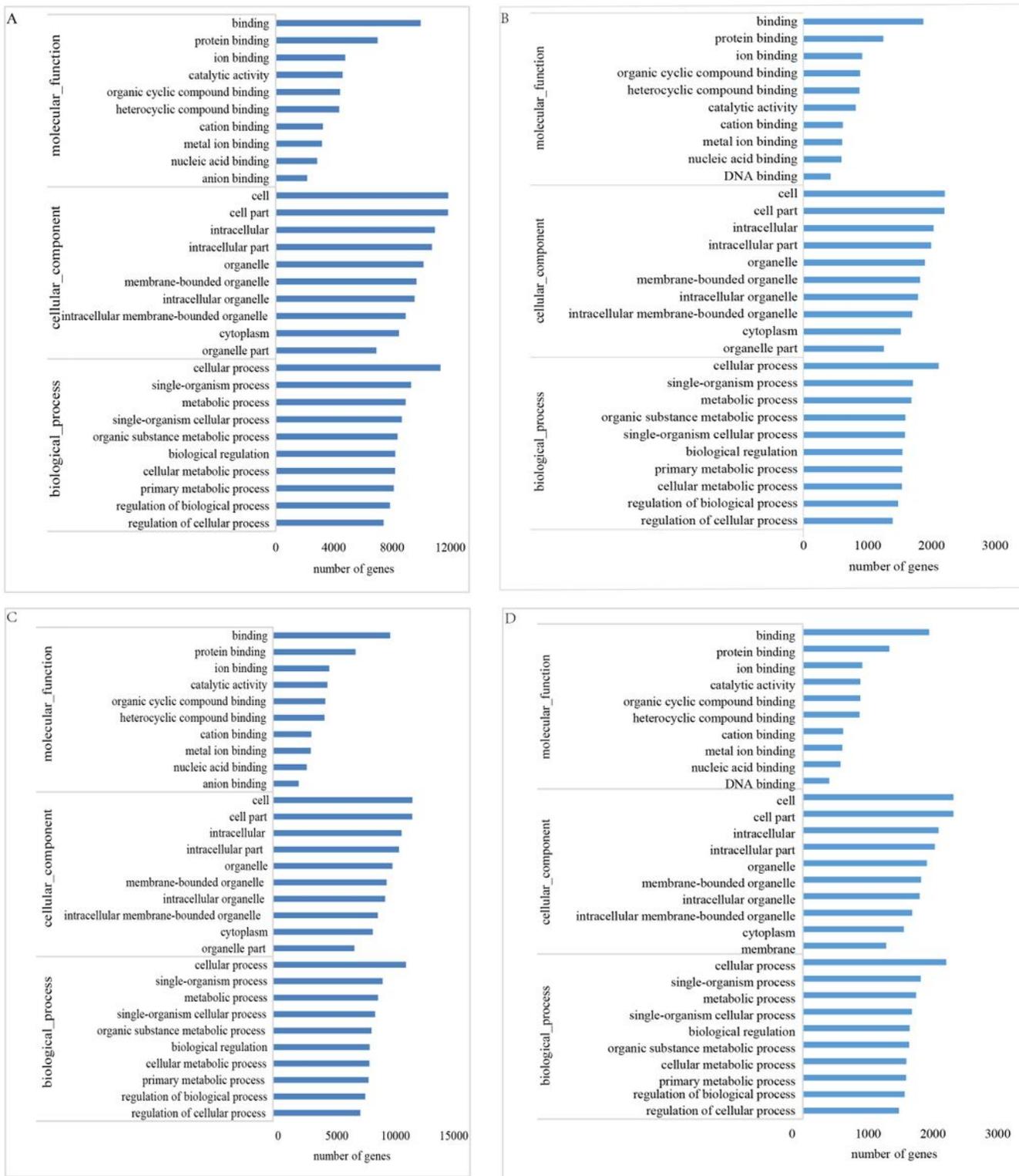
**Figure 2**

Venn diagram of peripheral blood and cord blood. Venn diagram of DElncRNAs (A), DEmiRNAs (B), and DEmRNAs (C).



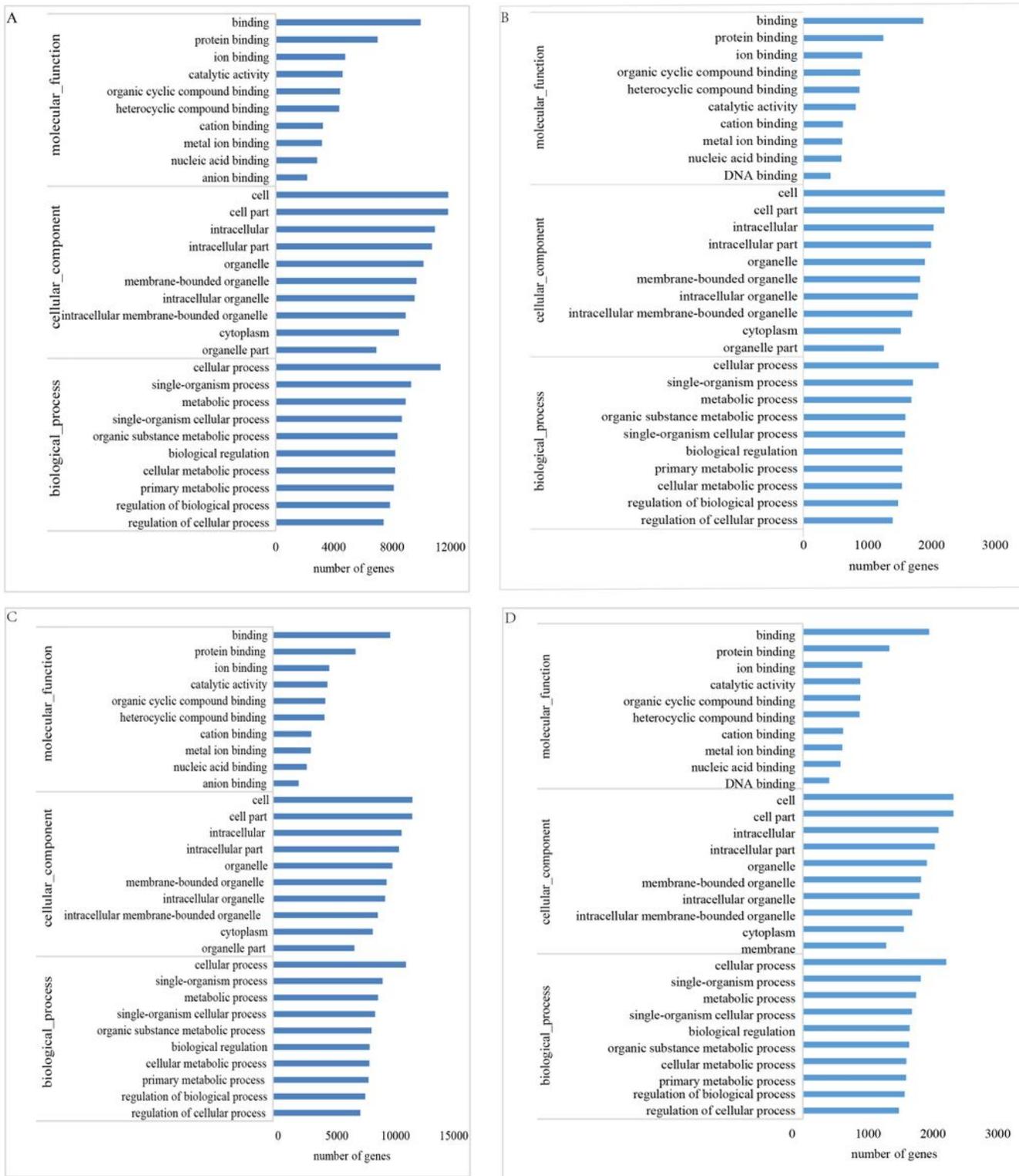
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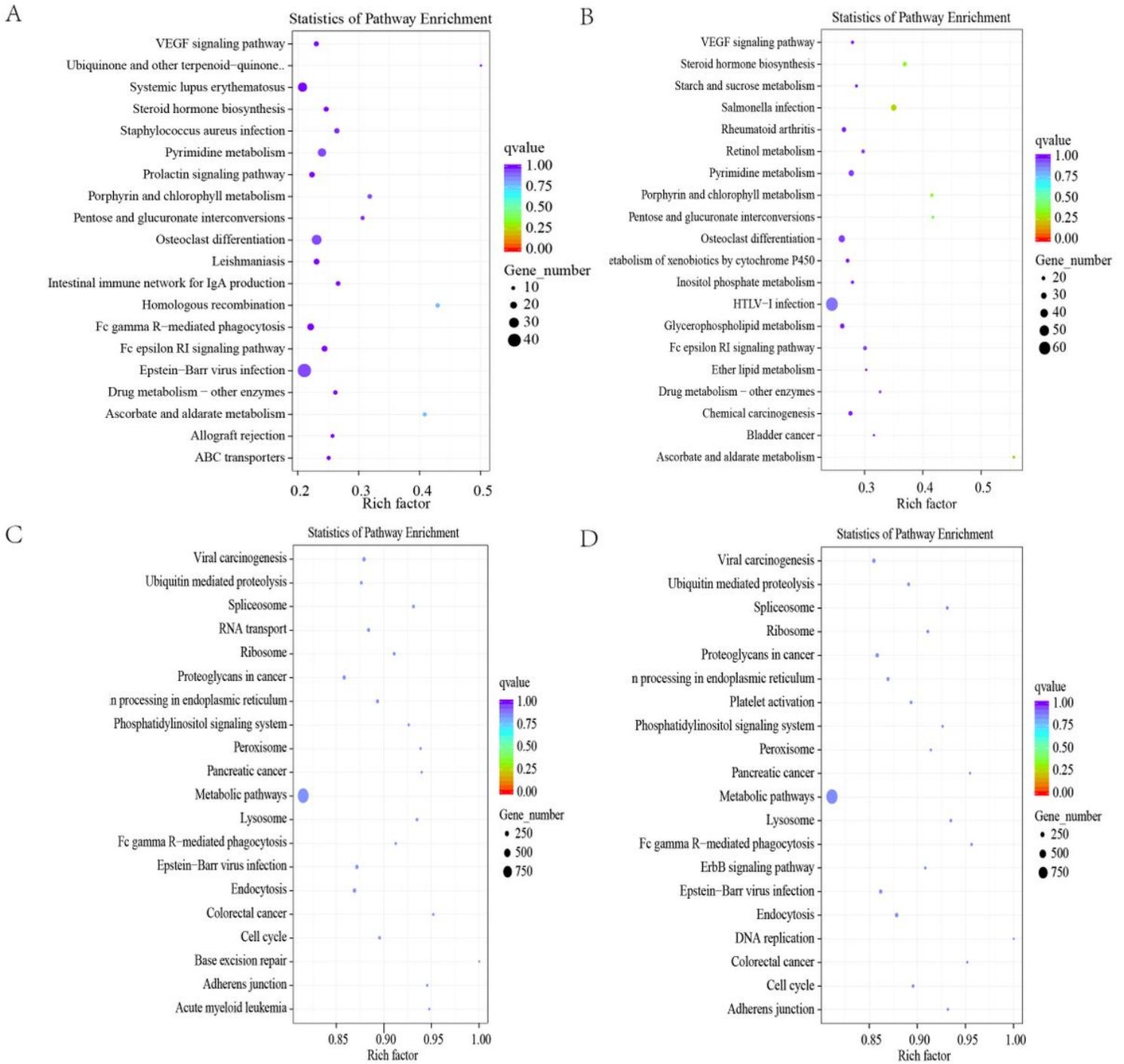
**Figure 3**

GO enrichment of DElncRNAs. Go terms of DElncRNAs co-expressed (A) and co-located (B) mRNAs in cord blood with top 10. Go terms of DElncRNAs co-expressed (C) and co-located (D) mRNAs in peripheral blood with top10.



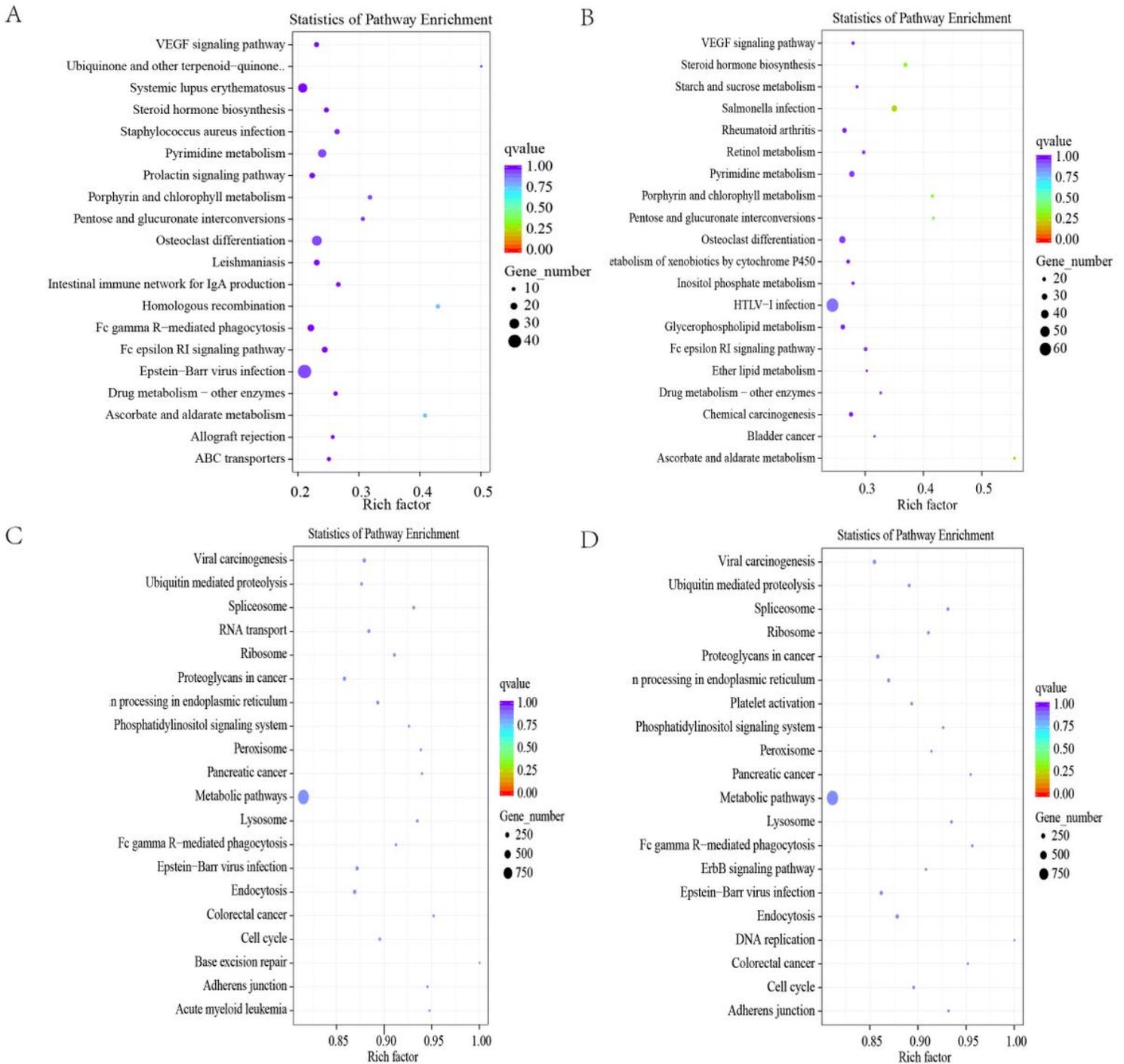
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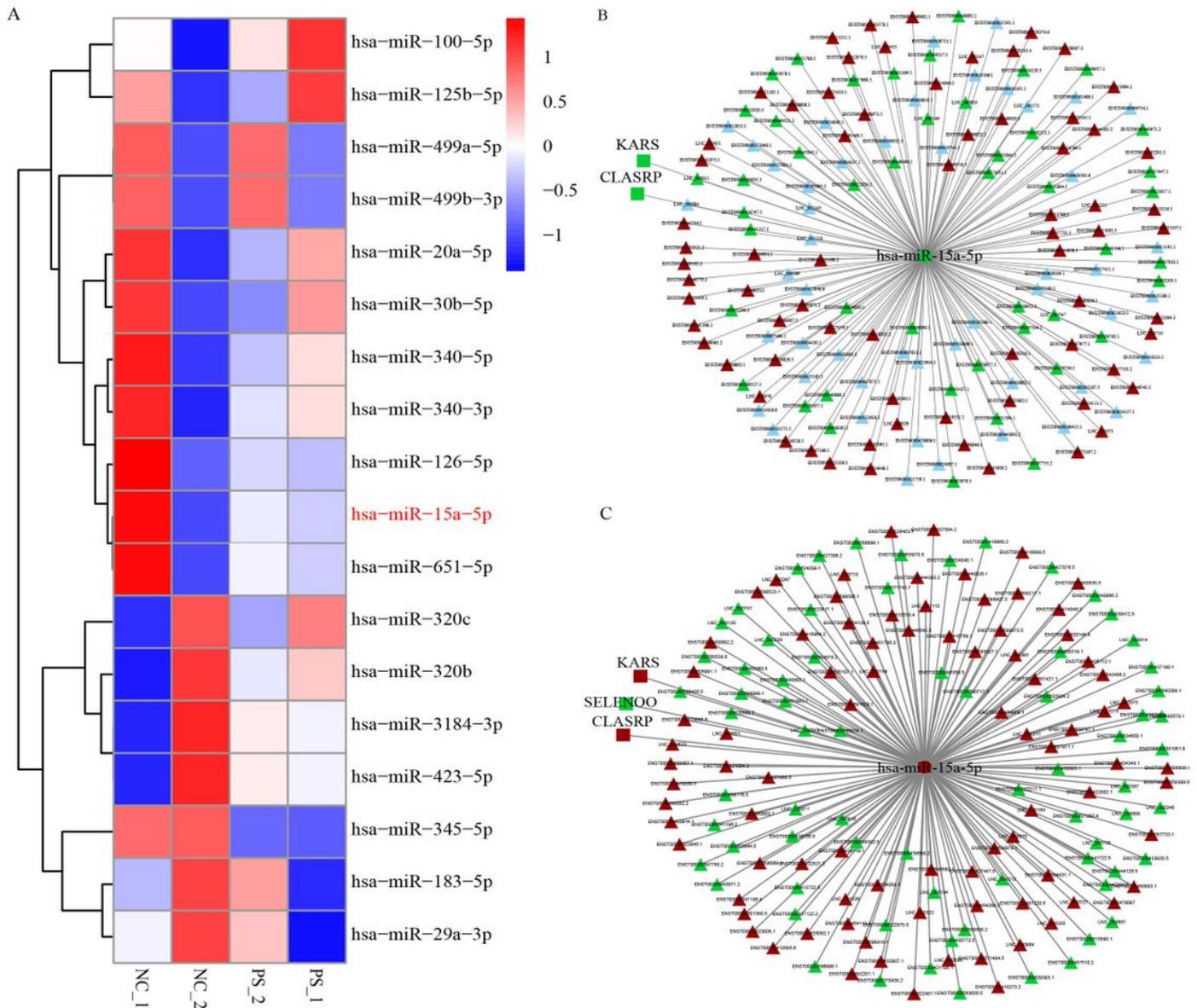
**Figure 4**

KEGG enrichment of DElncRNAs. KEGG enrichment of DElncRNAs co-expressed (A) and co-located (B) mRNAs in cord blood. KEGG enrichment of DElncRNAs co-expressed (C) and co-located (D) mRNAs in peripheral blood.



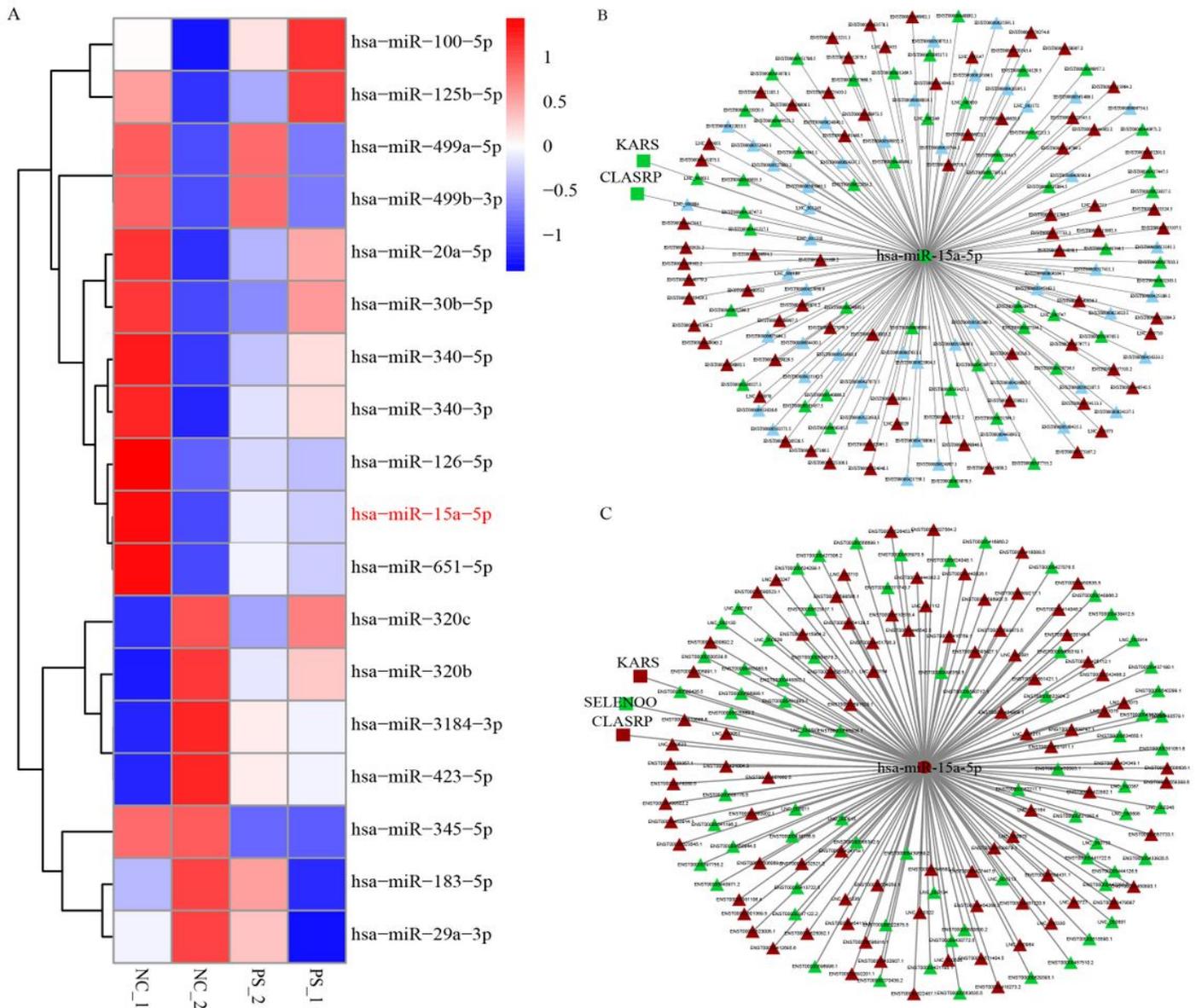
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**Figure 5**

Hierarchical clustering and DElncRNAs-DEmiRNA-DEmRNAs regulation network. Hierarchical clustering of DEmiRNAs (A). DElncRNAs-hsa-miR-5a-3p-DEmRNAs with a total of 163 DElncRNAs, 1 miRNA and 2 mRNAs in cord blood (B) and DElncRNAs-hsa-miR-5a-3p-DEmRNAs with a total of 157 DElncRNAs, 1miRNA and 3 DEmRNAs in peripheral blood (C).



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