Differentially expressed genes SNRPC and PRPF38A are potential biomarkers candidates for osteosarcoma

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Differentially expressed genes SNRPC and PRPF38A are potential biomarkers candidates for osteosarcoma

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Abstract

Background: Osteosarcoma (osteogenic sarcoma, OS) is a primary cause of morbidity and mortality and is associated with poor prognosis in the field of orthopedic. Globally, rates of OS are highest among 15 to 25-year-old adolescent. However, the mechanism of gene regulation and signaling pathway is unknown.

Material and Methods: GSE9508, including 34 OS samples and 5 non-malignant bone samples, was gained from Gene Expression Omnibus (GEO) database. The differentially expressed genes (DEGs) were picked out by GEO2R online R soft tool. Furthermore, the protein-protein interaction (PPI) network between the DEGs was molded utilizing STRING online software. Afterward, PPI network of DEGs was constructed. Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of DEGs were carried out on DAVID online tool and visualized via cytoscape software. Subsequently, module analysis of PPI was performed by using MCODE app. What's more, prognosis-related genes were screened by using online databases including GEPIA, UALCAN and cBioPortal databases.

Results: Totally, 671 DEGs were picked out, including 501 up-regulated genes and 170 down-regulated genes. Moreover, 22 hub genes were identified to be significantly

expressed in PPI network (16 up-regulated and 6 down-regulated). We found that spliceosome signaling pathway may provide a potential target in OS. Furthermore, on the basis of common crucial pathway, PRPF38A and SNRPC were closely associated with spliceosome.

Conclusion: This study showed that SNRPC and PRPF38A are potential biomarkers candidates for osteosarcoma.

Key words: PRPF38A, SNRPC, Osteosarcoma, GEO, DEGs

Introduction

The early detection of OS is limited. Most patients were diagnosed at a middle or advance stage. Therefore, it is very valuable to find a biomarker for evaluation of the of OS(*1-4*). Recently. High-throughput biochip technology has been prevalent in screening of pre-symptomatic disease(*5-7*). Bioinformatics have led to using for data-intensive statistical analysis in various fields of healthcare(*8-12*). Development of big-data has attracted attention in recent years(*13-16*). It provided new insights toward novel strategies for early testing and diagnosis of cancer(*17-20*). However, bioinformatics study of OS has not been catalogued. We tested GSE9508(Platform GPL676) from GEO. The dataset was divided into two part :34 OS sample and 5 non-malignant bone sample. Microarray dataset was downloaded from GEO and analyzed via GEO2R online tool. What' s more, DEGs between OS samples and non-malignant bone samples were screened by GEO2R. Moreover, DAVID version 6.8 (*21*)was used to analyze KEGG pathway and GO enrichment analysis with 501 up-regulated and 170 down-regulated DEGs. Multiple PPI network was calculated by using STRING online tool version 11.0(*22*). Furthermore, we establish simulation of PPI network with DEGs in Cytoscape software (version 3.7.2) (*23*)and then 23 core genes were picked out by MCODE app(*24*). Next, these genes were imported into (*25*) cBioPortal (*26*)databases for significant prognosis information($P<0.05$). However, only 8 genes were valid and then re-analyzed these central genes for KEGG pathway enrichment. Last but not least, PRPF38A and SNRPC were obtained and enriched in spliceosome pathway. The aim of present research was to provide a potential biomarker in OS.

Materials and methods

Microarray and DEGs. Microarray data containing OS related information were download from the GEO database (http://www.ncbi.nlm.nih.gov/gds/), including 34 OS samples and 5 non-malignant bone samples. A microarray dataset, GSE9508(GPL6076). Analyzed via GEO2R online R soft tool(*27*). DEGs were selected according to adjust P-value<0.05, logFC|>1. All data were preserved in excel format. On this basis, inclusion criteria for up-regulated was logFC>1. Likewise, logFC>-1 was considered as down-regulated.

GO and KEGG pathway enrichment analysis. Two common approaches for identifying molecular function and biological process as mentioned above. Functional enrichment analysis was performed DAVID Bioinformatics resources database version 6.8(*28*)(http://david .ncifcrf.gov/).

Protein-protein interaction. We cluster the DEGs PPI network to identify novel gene utilizing STRING online tool version 11.0(*22*) (https://string-db.org). Finally, the data were saved in tab-separated values (TSV format).

Central genes module analysis. Raw data files were imported into Cytoscape3.7.2, we run Molecular Complex Detection(MCODE)(*24*), an app of cytoscape, to calculate the significant modules in PPI network, with the threshold set as follows: Degree cutoff=2, Node Score Cut off=0.2, Max. Depth=100, K-core=0.2.

Overall survival of prognosis-related genes. Survival prediction was performed using cBioPortal(*26*)(http://www.cbioportal.org/). Statistical analyses for survival were performed with log rank test. A P-values less than 5% was considered as statistically significant. In addition, novel genes were pinpointed according to the threshold values above.

Result

Identification of DEGs in osteosarcoma. There were 34 OS samples and 5 non-malignant samples in our present research. Totally, 671 DEGs were picked up through GEO2R online R software tool, involving 501 up-regulated (namely logFC>1) and 170 down-regulated (namely logFC<-1) (Table I).

GO and KEGG pathway enrichment analysis. GO and KEGG pathway enrichment analysis was performed using DAVID database. Within the biological process (BP)

categories, nuclear-transcribed mRNA poly(A) tail shortening, vesicle fusion, cellular response to caffeine, female meiotic division, regulation of heart rate were dominant term for up-regulated DEGs. Down-regulated were particularly featured in translation, SRP-dependent cotranslational protein targeting to membrane, regulation of viral transcription, nuclear-transcribed mRNA catabolic process, nonsense-mediated decay, negative regulation of endopeptidase activity. For molecular function (MF)level, up-regulated genes included in transcription factor activity, sequence-specific DNA binding, nucleotide binding, extracellular matrix constituent, lubricant activity, poly(A) RNA binding, RNA polymerase II regulatory region sequence-specific DNA binding. However, down-regulated genes involved in structural constituent of ribosome, protein binding, histone methyltransferase activity, U1 snRNA binding, endopeptidase inhibitor activity. In the cellular component (CC)category, eukaryotic translation initiation factor 4F complex, nucleoplasm, dendrite, cytoplasmic microtubule, primary cilium were main enrichment term for up-regulated. Whereas, the down-regulated genes were involved in photoreceptor inner segment, blood microparticle, photoreceptor outer segment, ribosome, perinuclear region of cytoplasm (Table II). KEGG pathway analysis was shown that up-regulated genes mainly play a role in spliceosome(P-value<0.05). While the significance of identified pathway, down-regulated related, was ribosome(P-value<0.05) (Table III).

Protein-protein interaction. The DEGs were mapped to PPI network by using STRING (Fig. I). In addition, the network was identified via MCODE plugin in cytoscape software. Additionally, 23 central genes were screened, which include 16 up-regulated and 7 down-regulated (Fig. IIA and Fig. IIB).

Overall survival of prognosis-related genes. Analysis of central gene by using cBioPortal database. A total of 8 prognosis-associated genes were identified using overall survival analysis from above database (Table IVand Fig.III).

Re-analaysis of 8 central genes by KEGG pathway enrichment analysis. A subset of 8 genes, which related to prognosis, were selected for KEGG pathway enrichment analysis. The result of the cluster shows an enrichment for terms related to spliceosome, which SNRPC and PRF38A were directly involved in (Table V and Fig. IV).

Discuss

Early diagnosis and timely treatment contribute to improving the prognosis of sarcoma(*29-32*). In this study, we analyzed GSE9508 dataset downloaded from GEO database, and calculated 2 potential genes (SNRPC and PRPF38A) associated with OS through a serious of bioinformatics method. It is worth nothing that 671 DEGs were screened out after a comparative analysis between OS samples and non-malignant samples via GEO2R online R software(*33, 34*)(|logFC|>1 and adjust P<0.05) including 501up-regulated and170 down-regulated DEGs. After bioinformatical analysis of GO and KEGG pathway, we acquired that 1) for BP categories, up-regulated DEGs were featured in regulation of heart rate, vesicle fusion, nuclear-transcribed mRNA poly(A) tail shortening, cellular response to caffeine, female meiotic division were dominant term for up-regulated DEGs. Down-regulated were particularly enriched in regulation of viral transcription, translation, SRP-dependent cotranslational protein targeting to membrane, nuclear-transcribed mRNA catabolic process, nonsense-mediated decay, negative regulation of endopeptidase activity; 2) for MF, up-regulated genes included in transcription factor activity, sequence-specific DNA binding, nucleotide binding, extracellular matrix constituent, lubricant activity, poly(A) RNA binding, RNA polymerase II regulatory region sequence-specific DNA binding. However, down-regulated genes included in structural constituent of ribosome, protein binding, histone methyltransferase activity, U1 snRNA binding, endopeptidase inhibitor activity; 3) for CC, up-regulated DEGs were enriched in eukaryotic translation initiation factor 4F complex, nucleoplasm, dendrite, cytoplasmic microtubule, primary cilium were main enrichment term for up-regulated. Whereas, the down-regulated concentrated in photoreceptor inner segment, blood microparticle, photoreceptor outer segment, ribosome, perinuclear region of cytoplasm (Table II).

KEGG enrichment analysis provided details that up-regulated genes participated in spliceosome signaling. Based on the KEGG pathway, down-regulated gene were in ribosome (Table III, P<0.05). Though PPI network construction, 23 core genes were identified (involving 16 up-regulated and 6 down- regulated) via GEPIA and UALCAN and cBioPortal databases. A total of 8 genes significantly associated with prognosis

were screened.

Additionally, re-analysis 8 novel genes by using DAVID shown that SNRPC and PRPF38A as potential biomarkers and spliceosome had a significant, which provided a new effective target to improve the prognosis of OS patients.

Small nuclear ribonucleoprotein poly peptide C(SNRPC), is also known as U1 snRNP, which is important for recognition of pre-mRNA and assembly of spliceosome(*35, 36*). Another study proved that SNRPC is related to splice-site(*37*). Some of these protein interact with SNRPC(*38*). Moreover, Wang et al indicated that SNRPC, which is the main component of spliceosome(*39*). Lindén et al reported alternation in pre-mRNA spliceosome is a promising biomarker, which plays an important role in diagnosis of Stochastic Loewner Evolution (SLE)(*40, 41*).

Pre-mRNA splicing factor 38A (PRPF38A), is a center of spliceosome component, which is related to protein-protein interaction(*42*). Previous research proved that knock down of PRPF38A resulted in widespread intron retention (*43*). Whereas it was then demonstrated that knock down of PRPF38A promotes apoptosis in triple negative breast cancer(*44*).

To date, many studies confirm that SNRPC and PRPF38A were related to numerous types of cancer progression(*36, 45-48*). Nevertheless, studies were very few and far between in OS. Thus, these data may provide some functional information from bench to bedside.

Conclusions

In summary, our study presents SNRPC and PRPF38A were identified as potential biomarkers in OS by bioinformatical analysis. We provide a new strategy for osteosarcoma treatment, however, which should be verified in the future.

Abbreviations

OS: Osteosarcoma; GEO: Gene Expression Omnibus; DEGs: differentially expressed genes; PPI: protein-protein interaction; GO: Gene ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; MCODE: Molecular Complex Detection; BP :biological process; MF: molecular function; CC: cellular component; SNRPC: Small nuclear ribonucleoprotein poly peptide C; SLE: Stochastic Loewner Evolution;

PRPF38A: Pre-mRNA splicing factor 38A;

Ethical Approval and Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of supporting data

We declare that all data supporting our findings are provided in the manuscript.

Conflict of Interest

No conflict of interest declared.

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Authors' contributions

Dr. CY conceived and designed the study. CS contributed to data analysis and wrote the first draft of the manuscript.

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Figure I. Protein-protein interaction network showing experimentally verified and predicted interaction information among the proteins encoded by the differentially expressed genes.

Figure Ⅱ. A sub-network of key proteins was constructed by using Cytocape. Yellow and blue depict the up- or down-regulated differentially expressed genes, consecutively.

Figure Ⅲ Prognostic survival analysis of CDC34, HNRNPA3, SRRT, HNRNPD, LRRC41, PRPF38A, SNRPC and KLHL22 genes via cBioPortal database. CDC34, cell division cycle 34; HNRNPA3, heterogeneous nuclear ribonucleoprotein A3; SRRT, serrate RNA effector molecule; HNRNPD, heterogeneous nuclear ribonucleoprotein D; LRRC41, leucine rich repeat containing 41; PRPF38A, pre-mRNA processing factor 38A; SNRPC, small nuclear ribonucleoprotein polypeptide C; KLHL22, kelch like family member 22.

Figure Ⅳ Significantly enriched pathway terms of DEGs in osteosarcoma. KEGG pathway annotations of the spliceosome pathway. Red star-marked means significant genes.

Table Ⅰ All 671 DEGs were detected from GSE9508, involving 501 up-regulated and 170 down regulated genes in OS samples compared to non-malignant sample.

Table Ⅱ GO enrichment analysis of DEGs in osteosarcoma.

Table Ⅲ KEGG enrichment analysis of DEGs in osteosarcoma.

Table Ⅳ The prognosis-related information of 23 central genes.

Table Ⅴ KEGG pathway enrichment analysis with 2 novel genes.

Figures

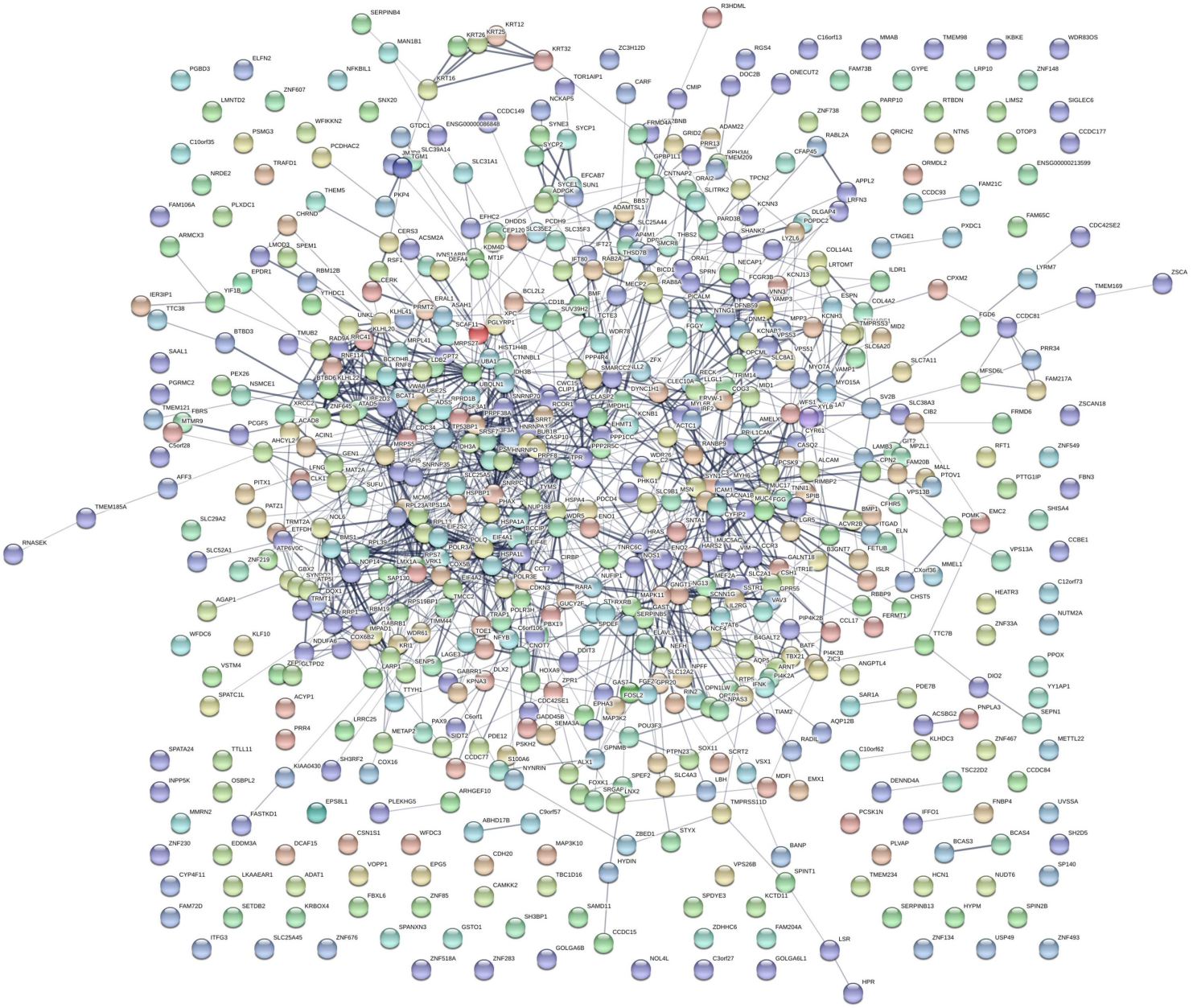

Figure 1

Protein-protein interaction network showing experimentally verified and predicted interaction information among the proteins encoded by the differentially expressed genes.

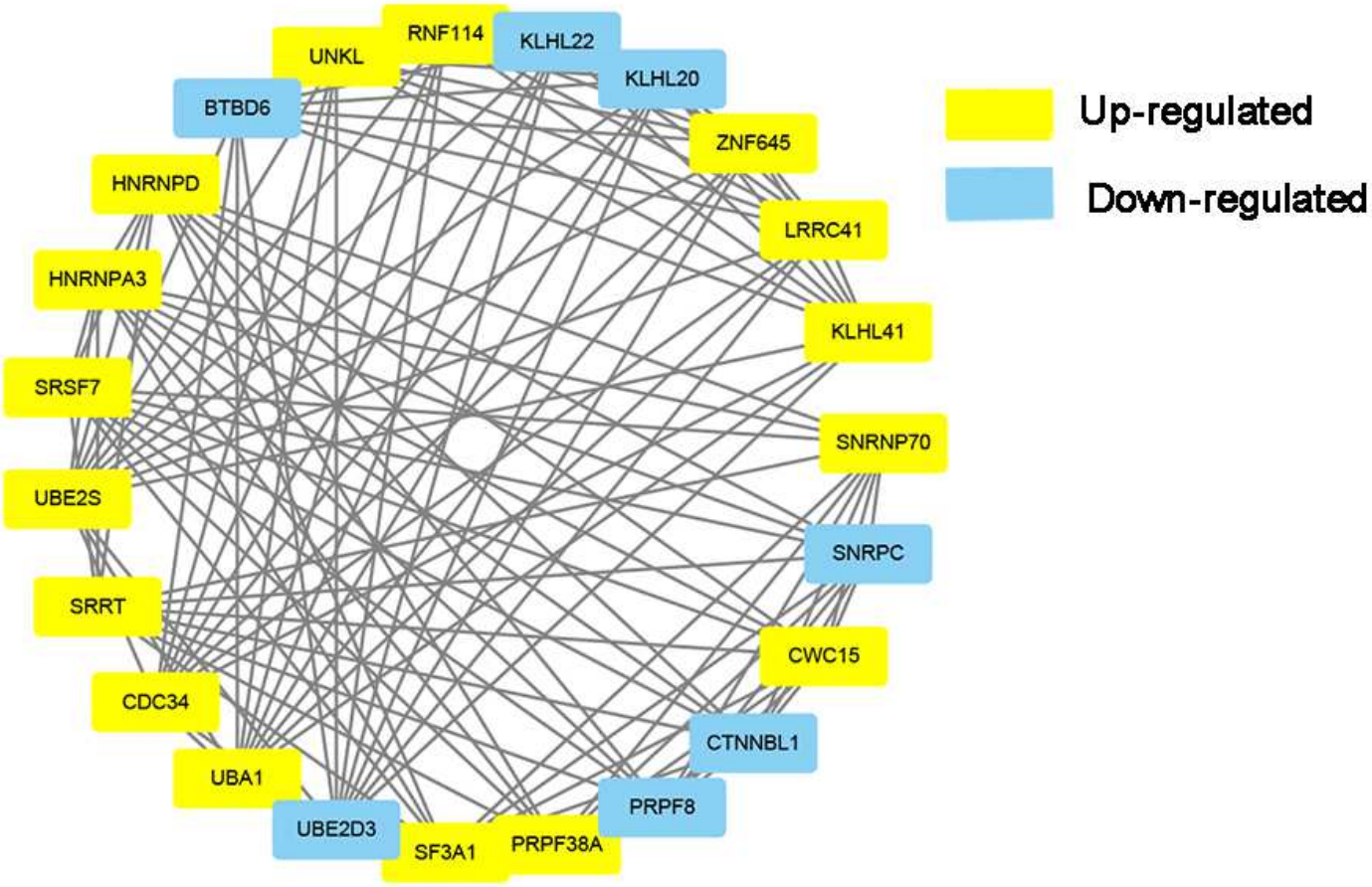

Figure 2

A sub-network of key proteins was constructed by using Cytocape. Yellow and blue depict the up- or down-regulated differentially expressed genes, consecutively.

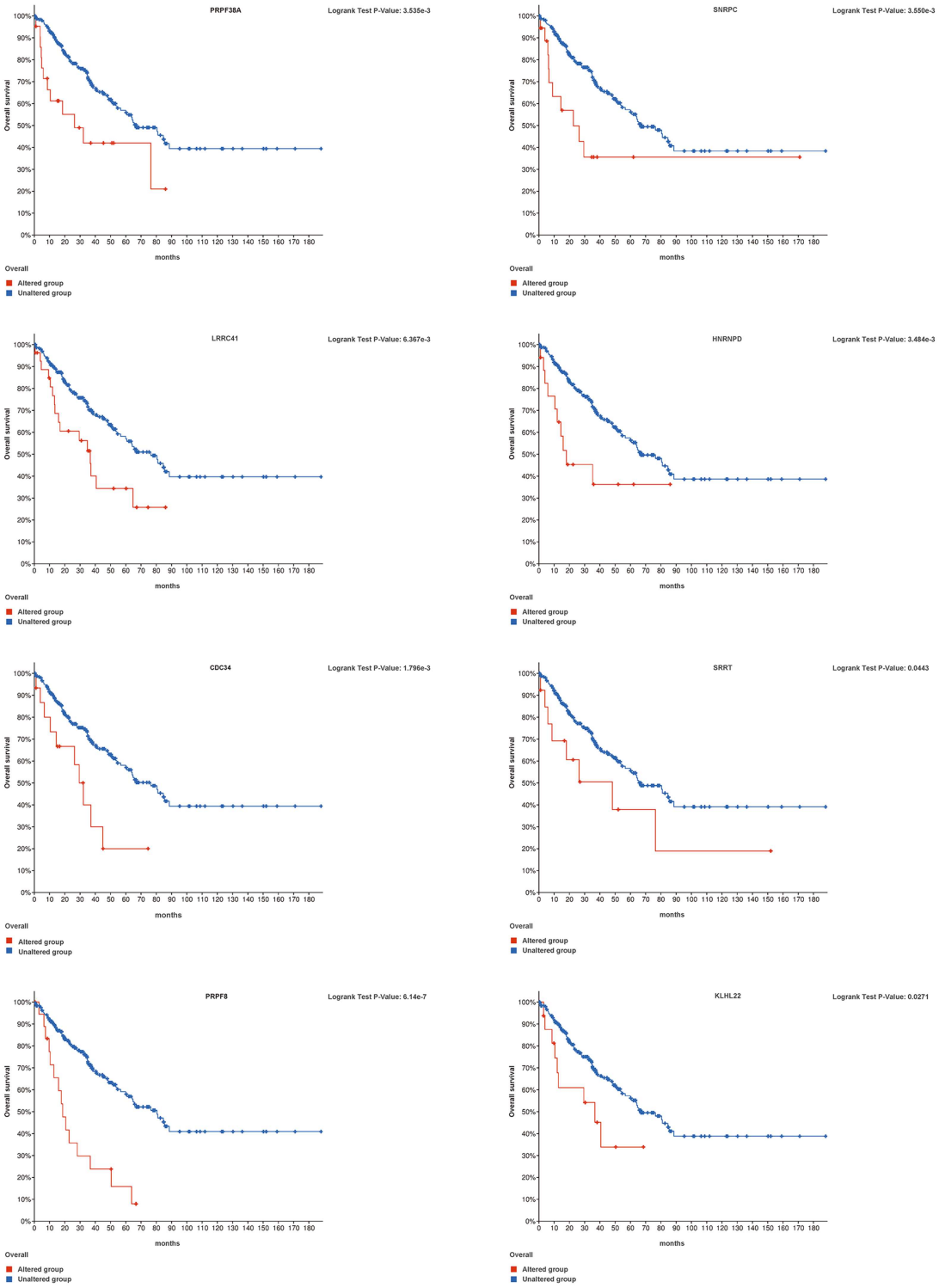

Figure 3

Prognostic survival analysis of CDC34, HNRNPA3, SRRT, HNRNPD, LRRC41, PRPF38A, SNRPC and KLHL22 genes via cBioPortal database. CDC34, cell division cycle 34; HNRNPA3, heterogeneous nuclear ribonucleoprotein A3; SRRT, serrate RNA effector molecule; HNRNPD, heterogeneous nuclear ribonucleoprotein D; LRRC41, leucine rich repeat containing 41; PRPF38A, pre-mRNA processing factor 38A; SNRPC, small nuclear ribonucleoprotein polypeptide C; KLHL22, kelch like family member 22.

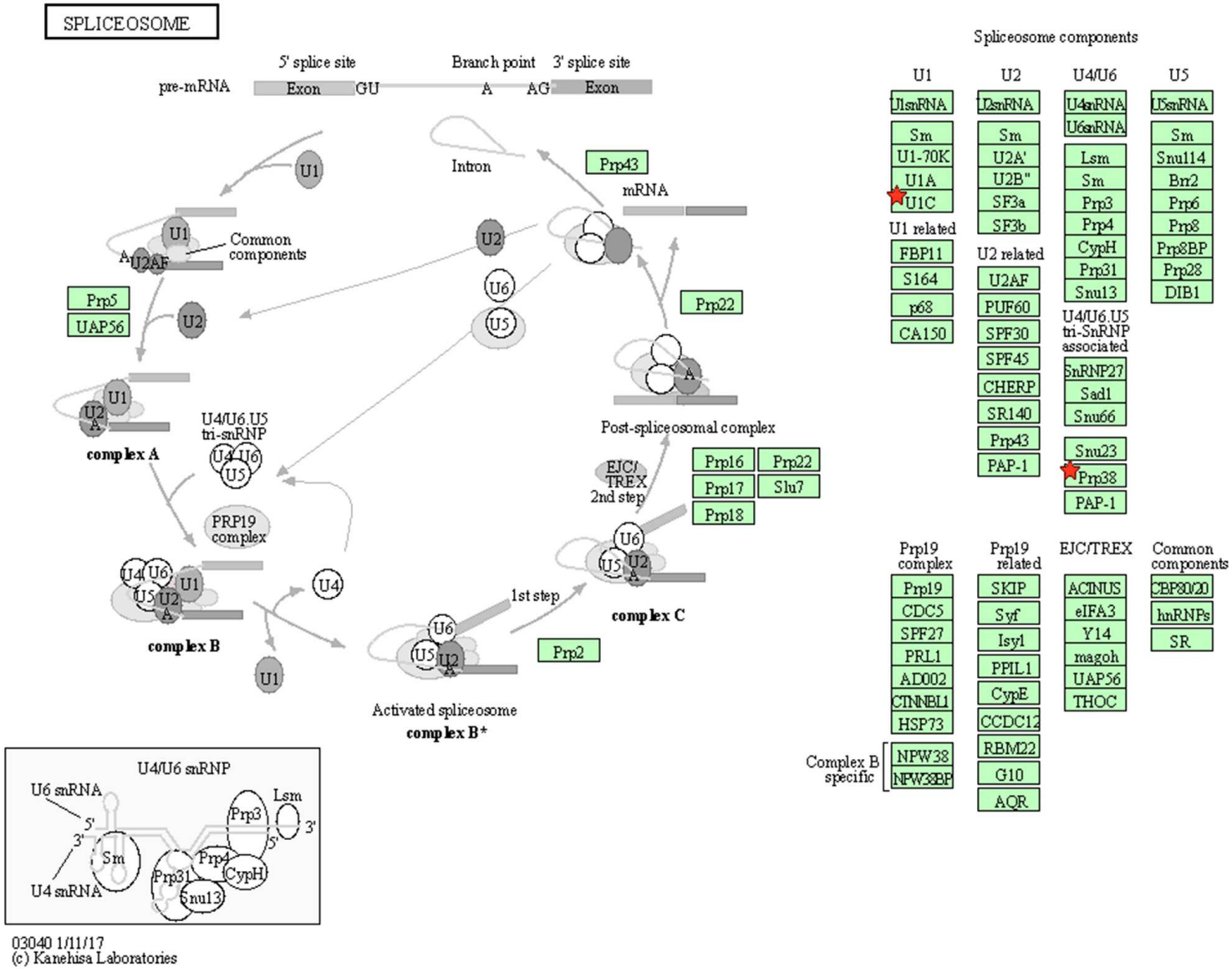

Figure 4

Significantly enriched pathway terms of DEGs in osteosarcoma. KEGG pathway annotations of the spliceosome pathway. Red star-marked means significant genes.

Supplementary Files

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