KIF11 Might be a Novel Biomarker for Bone Metastasis of Prostate Adenocarcinoma

Haoyuan Wang

Hebei Medical University Fourth Affiliated Hospital and Hebei Provincial Tumor Hospital

Sijie Li

Hebei Medical University Fourth Affiliated Hospital and Hebei Provincial Tumor Hospital

Bin Liu

Hebei Medical University Fourth Affiliated Hospital and Hebei Provincial Tumor Hospital

Shufei Wei

Hebei Medical University Fourth Affiliated Hospital and Hebei Provincial Tumor Hospital

Tianyi Wang

Hebei Medical University Fourth Affiliated Hospital and Hebei Provincial Tumor Hospital

Tao Li

Hebei Medical University Fourth Affiliated Hospital and Hebei Provincial Tumor Hospital

Jiahu Lin

Hebei Medical University Fourth Affiliated Hospital and Hebei Provincial Tumor Hospital

Aili Zhang

Hebei Medical University Fourth Affiliated Hospital and Hebei Provincial Tumor Hospital

Xiaochen Ni (✉ ssymwnxc@163.com)

Hebei Medical University Fourth Affiliated Hospital and Hebei Provincial Tumor Hospital

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Research

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Abstract

Background: A serious issue derived from Prostate adenocarcinoma (PCa) is its propensity to metastasize to bone, which occurred in up to 90% of patients with advanced PCa. The kinesin superfamily (KIFs) is well-documented oncogenic protein implicated mainly in chromosomal and spindle movements and are involved in some cellular activities, such as mitosis, transport of vesicles, organelles, and mRNAs. However, the clinical significance and biological roles of KIF in bone metastasis of PCa still need further exploration.

Method: We download three datasets from the Gene Expression Omnibus (GEO) data repository. Firstly, we merge the three datasets, and then obtain the gene modules most relevant with clinical traits (morbidity of the bone metastasis of PCa) by “WGCNA” R package. Functional enrichment analysis was performed by the DAVID tool and Metascape. Differentially expressed genes (DEGs) between bone metastasis of PCa and primary PCa tissue samples were identified by “limma” R package. Then we intersect the gene module with DEGs. Protein-protein interaction (PPI) network was constructed by Cytoscape, and hub genes were excavated. Immunohistochemistry (IHC) image was downloaded from The Human Protein Atlas (www.proteinatlas.org) to verify the feasibility of the target molecular marker identified by bioinformatics and statistical analysis.

Result: 16 gene modules were obtained through WGCNA analysis and the tan module is most related to the occurrence of bone metastasis, containing 147 genes. Thus, we selected the tan module for further analysis. 877 DEGs were detected by limma package of R software. After taking the intersection of the DEGs and tan module, we got 51 common genes. Protein-protein interaction network (PPI) was constructed for the 51 genes. 7 hub genes (BUB1, KIF2C, RACGAP1, CENPE, KIF11, TTK, KIF20A) were identified from the common results of four different algorithms (Betweenness, Closeness, Eccentricity, and Radiality). Survival analysis based on disease free survival (DFS) was carried out for the 7 hub genes, and all of them have significant poor prognostic performance ($P < 0.05$). And the bubble charts were plotted for functional annotation of the miRNA which can be the regulating factors of the hub genes. Univariate and multivariate logistic regression analysis were performed for screening the independent risk factors of the bone metastasis of PCa, and KIF11 was finally obtained. The immunohistochemical image of bone metastasis of PCa was obtained on the protein Atlas, which showed a strong positive expression of KIF11.

Conclusion: In current study, molecules strongly correlated with the occurrence of bone metastasis of PCa were excavated. And provide the evidence that KIF11 may serve as a potential bone metastasis marker in PCa, which might be used for the guidance of clinical practice.

Introduction

Prostate adenocarcinoma (PCa) is the most frequently diagnosed cancer in 105 countries (36 cancers in 185 countries) and the most common cause of death due to malignancy among men^[1]. Based on data

obtained from 2010–2014, the number of new cases of PCa was 119.8 per 100,000 men per year and the number of deaths was 20.1 per 100,000 men per year in America^[2, 3]. Based on statistical models for analysis, death from PCa mainly due to metastasis when cancer cells spread to other areas of the body such as the pelvic and retroperitoneal lymph nodes, the spinal cord, bladder, rectum, bone and brain. Bone metastasis is the most serious type of metastasis PCa^[4]. Unlike liver, lung or brain tissues, bone marrow contains less arterial blood flow. Thus, the hemodynamics determining metastatic colonization may not be important organ-specific factors contributing to bone metastasis. The development of bone metastasis is a multi-step process, including colonization (circulating cancer cells enter the bone marrow compartment), dormancy (cancer cells adapting to the bone microenvironment and remaining dormant for a long period of time), reactivation and development, cancer cells changing from the dormant state to an active proliferation state reconstruction, and cancer cells changing the original bone structure and function^[5, 6]. After bone metastasis occurs, the malignant proliferation rate of cancer cells is significantly accelerated under the influence of the growth factors released from the bone. Bone metastasis in advanced PCa is often fatal. Therefore, it is urgent to explore the potential mechanism of bone metastasis in PCa.

Intracellular transport is fundamental for cellular function, survival and morphogenesis. Kinesin superfamily proteins (also known as KIFs) are important molecular motors that directionally transport various cargos, including membranous organelles, protein complexes and mRNAs^[7]. The mechanisms how different kinesins recognize and bind to specific cargos, as well as how determine the direction of transport and kinesins unload cargo, have already been revealed^[8–10]. And KIFs also play an important role in the process of tumor proliferation, invasion and metastasis. Li et al. reported KIF2C/4A/10/11/14/18B/20A/23 predict poor prognosis and promote cell proliferation in hepatocellular carcinoma^[11]. Sun et al. also reported the KIF21B act as an oncogene in non-small cell lung cancer by regulating the metastasis progress^[9]. Research by Zhou et al. showed KIF11 is associated with poor outcomes from breast Cancer as an oncogene.^[12] Piao et al. reported that the expression of KIF11 predicts aggressiveness of PCa^[13]. Therefore, we speculate that the abnormal expression of KIF11 in PCa is related to its bone metastasis.

Bioinformatic is an emerging research method that can analyze and explore massive amounts of information. It is widely used in the functional analysis of DNA, RNA and proteins and is of great significance for guiding clinical work^[14].

We used bioinformatics method to screen and enrich the differently expressed genes in bone metastasis PCa, and selected 7 hub genes (CENPE, KIF2C, BUB1, KIF11, KIF20A, TTK, RACGAP1). And the 7 hub genes were included in univariate and multivariate logistic regression analysis to identified independent prognostic factor which correlated with disease free survival time (DFS) of bone metastasis PCa patients, and finally KIF11 was screened out. In this study, our results clarify the underlying mechanism to determinate the role of KIF11 in bone metastasis PCa.

Methods

Data collection

The raw expression profile was downloaded from Gene Expression Omnibus (<https://www.ncbi.nlm.nih.gov/geo/>, GEO) for comparing gene expression between PCa bone metastasis tissues and primary PCa tissues. The gene expression data of GSE32269, GSE74367, and GSE77930 were download based on the platform of GPL147, GPL15659, GPL21289. The three datasets included 63 bone metastasis PCa samples, 388 primary PCa samples. And the clinical information of corresponding sample was available.

Data Processing

Robust multi-array average (RMA) was used to correct and normalize the raw expression data of each dataset. Then merge the three datasets by Perl programming language (<https://www.perl.org/>). The “SVA” package of R soft was conducted to eliminate batch effects and other unrelated variables in high-throughput experiments.

Co-Expression Network Construction

We used R package “WGCNA” to construct gene co-expression network in datasets. The soft-thresholding power β was calculated in the construction of each module using the pickSoftThreshold function of the WGCNA. Power value was screened using gradient algorithm to test the independence and the power value of different modules ranges from 1 to 20. After determining suitable power value when the index value for the reference dataset exceeded 0.8, the gene modules were constructed. The minimum number at 30 was set for each module, and the heatmap tool package was used to analyze and visualized the strength of correlation between each module. In order to generate dendrogram plot, a cut-line (0.25) was chosen.

Construction of module-clinic trait relationships

Modules form WGCNA were identified according to gene expression similarities in samples. In order to acquire the interested module, the relationship between clinical traits (occurrence of bone metastasis of PCa or not) and each module was calculated. The gene module most significantly correlated with “type”, namely bone metastasis or not in PCa, was retained for next step.

Functional Enrichment Analysis of genes from interested module

Metascape (<http://metascape.org>) is a free, well-maintained, user-friendly gene-list analysis tool for gene annotation and analysis. It is an automated meta-analysis tool to understand common and unique pathways within a group of orthogonal target-discovery studies. In this study, Metascape was used to conduct pathway and process enrichment analysis of the gene module most relevant to clinical traits screened out in WGCNA. GO enrichment analysis mainly described the biological processes (BP), cellular

components (CC) and molecular functions (MF) correlated with module genes. Information on the role and function of modular genes were enriched based on the Metascape online tool. Only terms with P-value < 0.05, minimum count of 3, and enrichment factor of >1.5 were considered as significant.

Screening of Differentially Expressed Genes

The differentially expressed genes (DEGs) of bone metastasis of PCa and primary PCa tissues were detected by “Limma” package of R software, use cut-off criteria as P-value < 0.05 and absolute $|\log FC| > 1$. Then, overlap the DEGs and the interested module from WGCNA to obtain the common DEGs.

Construction of Protein-Protein Interaction and selection of hub genes

Protein-protein interaction network (PPI) was constructed by the STRING online database (<http://string-db.org>) and imported into Cytoscape software for visualization and subsequent analysis. We used four algorithms (Betweenness, Closeness, Eccentricity and Radiality) in cytoscape to calculate top 10 hub genes respectively. Venn plot was performed to obtain the common hub genes.

Identification of hub genes associated with tumor

Comparative toxicogenomics database (<http://ctdbase.org/>, CTD database) is a web-based database that could provide the relationship between gene, protein and disease. In our study, the relationships between gene products and malignancy were analyzed by this database.

MiRNA Predicting and Functional annotation

TargetScan (www.targetscan.org) was an analysis tool, which could perform predictive analyses and determine potential mechanisms of co-regulation of the expression of hundreds of genes expressed in different cell types. In our study, the miRNAs that regulate the hub genes were screened out with TargetScan. DIANA-miRPath v3.0 (<http://www.microrna.gr/miRPathv3>) was an online software suite dedicated to construct functional and pathway enrichment analysis for miRNA. GO and KEGG pathway enrichment analysis of miRNAs that regulate the hub genes were performed using miRPath (P<0.05).

Survival analysis

Gene Expression Profiling Interactive Analysis (GEPIA, <http://gepia.cancer.pku.cn/>) is a web server based on data from the UCSC Xena program. The functions of the database are divided into two main themes: expression analysis and custom data analysis, which can be used to analyze gene expression differences between various cancers and normal tissues, and overall survival, etc. GEPIA database can be used to analyze Disease-Free Survival (DFS) between samples with high expression of hub genes and samples with low expression. The Kaplan–Meier (K-M) curve of the hub genes was plotted through the GEPIA database. The critical condition was set to logrank p-value<0.05. **Univariate and multivariate regression**

We obtained the immunohistochemical image of hub gene in to verify the hub gene related to bone metastasis PCa through in The Human Protein Atlas. Univariate and multivariate logistic regression analysis were performed for screening the independent risk factors of the bone metastasis of PCa.

Statistical Analysis

To investigate the relationship between hub genes and PCa bone metastasis, univariate and multivariate logistic proportional hazard regression analyses was conducted. Then, the independent risk factors of PCA patients with bone metastasis can be determined according to the results of multivariate analysis. All the statistical methods were conducted by the SPSS 22.0 software. “ $P < 0.05$ ” was used as the threshold value.

Results

GEO dataset

The three datasets (GSE32269, GSE74367 and GSE77930) we downloaded from GEO database include 63 PCa samples with bone metastasis and 388 primary PCa samples in total. GSE32269 based on the GPL147, includes 30 samples with bone metastasis of PCa and 25 primary PCa samples. GSE74367 based on the GPL15659, includes 76 primary PCa samples. GSE77930 based on the GPL21289, includes 33 samples with bone metastasis of PCa and 287 primary PCa samples. As shown in Table1

Weighted Genes Co-expression Network Construction Analysis

The 63 bone metastasis PCa patients and 388 primary PCa patients were included in the analysis. The results of sample hierarchical clustering analysis showed that there were no obvious outliers, and all 451 samples were included in the co-expression network analysis. In this study, the dynamic shear tree method was used to initially identify modules and merge similar modules. The minimum number of genes in the module was set to 30, and 16 corresponding modules were finally determined (Fig.1 A-E). Subsequently, clinical information (the occurrence of PCa bone metastasis) was imported, and the correlation coefficient between each module and PCa bone metastasis was calculated (Fig.1 F). The results showed that the module tan was most related to PCa bone metastasis ($\text{cor}=0.26$, $p=0.008$), including 147 genes. Therefore, the module tan was selected for further analysis.

Functional Enrichment Analysis

We used GO and KEGG function enrichment analysis to explore the potential functions and pathways of the genes in the tan module on the Metascape. The GO analysis results show that the genes in module tan mainly regulate cell cycle phase transition, cell division, spindle, chromosomal region, DNA repair. And KEGG pathway analysis mainly enrich in cell cycle, DNA replication, HTLV-I infection, base excision repair, progesterone-mediated oocyte maturation, etc. (Fig.2 A-F).

Selection of Differentially Expressed Genes

All of the 63 PCa samples with bone metastasis and 388 primary PCa samples were included in the differential expression analysis. A total of 877 DEGs were screened and their volcano plot and heat map were plotted (Fig.3 A and B). Venn plot was performed to overlap 51 common genes between the DEGs and tan model genes (Fig.3 C).

Construction of Protein-Protein Interaction and Selection of Hub Genes

We used the String website and Cytoscape software to construct a PPI network for the 51 common genes (Fig.3 D). Four different algorithms (Betweenness, Closeness, EcCentricity, and Radiality) were used to calculate the hub genes respectively, and the common hub genes of the four different algorithms were obtained (Fig.3 E). Finally, we got 7 hub genes (BUB1, KIF2C, RACGAP1, CENPE, KIF11, TTK, KIF20A; Table 2, Fig.3 F).

Identification of hub genes associated with tumor

In the results of CTD analysis, the 7 hub genes all have a strong correlation with nerve-related malignancy (Fig.4).

MiRNA Predicting and Functional annotation

We predicted miRNAs which regulate the 7 hub genes by the TargetScan (Table 3), and analyzed them on DIANA-miRPath v3.0 for BP, CC, MF, and KEGG functional annotation, and plotted four bubble charts respectively. The results of BP function analysis enriched in biological process, transcription initiation from RNA polymerase promoter and enzyme regulator activity. The results of CC function analysis enriched in cellular component, catabolic process and viral process. The results of MF function analyses enriched in molecular function Fc-epsilon receptor signaling pathway and cytosol. The results of KEGG pathway analysis enriched in TGF-beta signaling pathway MAPK signaling pathway and neurotrophin signaling pathway. (Fig.5 A-D).

Survival Analysis

We used the GEPIA website to analyze the DFS of the 7 hub genes. Results showed that all of the 7 gens, including CENPE (Logrank-P=0.00083, HR=2.7), KIF2C (Logrank-P=6.2e-5, HR=3.5), BUB1 (Logrank-P=0.00077, HR=2.1), KIF11 (Logrank-P=0.0079, HR=2.1), TTK (Logrank-P=0.028, HR=1.9), KIF20A (Logrank-P=0.001, HR=2.1) and RACGAP1 (Logrank-P=0.0019, HR=2.5) and were all significantly related with DFS (Fig.6 A).

Expression of KIF11

We downloaded the immunohistochemical image of KIF11 in bone metastasis PCa through The Human Protein Atlas. KIF11 has a strongly positive expression in PCa tissue which accompanies bone metastasis (Fig.6 B).

Statistical analysis

We conducted univariate and multivariate logistic proportional hazard regression analyses for the 7 hub genes, the results of univariate regression showed that KIF11 ($P=0.038$, $OR=2.331$, $95\%CI=1.049-5.178$) and KIF20A ($P=0.004$, $OR=0.108$, $95\%CI=0.024-0.493$) are both significantly correlated with the bone metastasis of PCa (Table4). And the results of multivariate regression indicated that only KIF11 ($P=0.038$, $OR=2.331$, $95\%CI=1.049-5.178$) can be the independent factor which influence the bone metastasis of PCa significantly (Table 5).

Discussion

According to Kamiya et al. research^[15], bone is a frequent site for metastasis in patients with advanced solid tumors, such as breast, lung, thyroid and renal cancers. And bone metastasis is the most metastasis type in prostate tumor. Bone metastasis occurs in approximately 80% of patients with advanced PCa^[16]. Skeletal-related events have been correlated with reduced survival and quality of life of patients with PCa^[15]..

KIFs are mainly involved in the intracellular transport process of various cell types^[17]. KIF11 (kinesin family member 11), also known as kinesin-5, is a molecular motor protein that essential in mitosis. It mediates centrosome separation and formation of the bipolar mitotic spindle, driving mitosis in order to support cell proliferation^[18, 19]. Inactivation of KIF11 results in inappropriate cell division and cell cycle arrest during mitosis, eventually leading to apoptosis. KIF11 also appears to have non-mitotic functions as well. It has also been proved to regulate axonal branching and growth cone motility and, more recently, shown to be involved in cell motility. KIF11 has been demonstrated to over-express in various malignancies and correlated with poor prognosis. The research in breast cancer showed that migration and invasion ability were decreased after inhibition of KIF11. KIF11 inhibitor significantly also reduced the tumor volume. In addition, Daigo et al. reported that strong KIF11 expression was significantly associated with poor prognosis among oral cancer patients^[20].

WGCNA analysis can not only find the correlation between genes and clinical traits, but also can quantitatively analyze the strength of the correlation between genes^[19]. We performed WGCNA analysis based on three datasets, and selected the most related to the occurrence of PCa bone metastasis^[21]. We used metaspape to perform functional enrichment and pathway analysis on the tan module, and the genes of the module mainly focused on cell cycle phase transition, cell division, spindle, chromosomal region, DNA repair, Cell cycle, DNA replication, HTLV-I infection, Base excision repair, Progesterone-mediated oocyte maturation. Then, we screened the differentially expressed genes (DEGs) for the three datasets, and overlapped the DEGs and the tan modular to obtain the common genes. PPI of the common genes was constructed and four algorithms (Betweenness, Closeness, Eclentricity and Radiality) were plotted to calculate top10 hub genes respectively. After intersecting the 10 hub genes from 4 independent algorithms, 7 hub genes were obtained. The function enrichment analysis of the miRNAs that regulate the 7 hub genes mainly affect the T biological process, transcription initiation from RNA polymerase promoter, enzyme regulator activity. cellular component, catabolic process, viral process.

molecular function Fc-epsilon receptor signaling pathway, cytosol. TGF-beta signaling pathway MAPK signaling pathway and neurotrophin signaling pathway.

After obtaining the hub genes, survival analysis was performed for the 7 hub genes and found that they were all related with DFS. Then the univariate and multivariate logistic proportional hazard regression analyses was performed for the 7 hub genes, and only KIF11 show as an independent risk factor for bone metastasis PCa. In the immunohistochemical image, KIF11 is strongly positively express in PCa bone metastasis tissue. So KIF11 may be a novel prognostic biomarker and guide future clinical practice and treatment.

In conclusion, the findings of this current study improve our understanding of the molecular mechanisms underlying bone metastasis of PCa. And KIF11 might promote bone metastasis and be a novel prognostic biomarker for patients with bone metastasis PCa, which can guide future clinical practice.

Declarations

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study complied with the Declaration of Helsinki and was approved by Ethics Committees of The Fourth Affiliated Hospital of Hebei Medical University.

Conflicts of interest

All the authors declare that they have no competing interests.

Consent for publication

The authors have no interests ethical, legal and financial conflicts related to the article. All authors read and approved the manuscript for publishing.

Availability of Data and Materials

All the data was available from GEO database (<https://www.ncbi.nlm.nih.gov/geo/>), and we are willing to provide our analysis data.

Authors' contributions

(I) Conception and design: Haoyuan Wang and Xiaochen Ni.

(II) Administrative support: Bin Liu, Aili Zhang and Shufei Wei.

(III) Collection and assembly of data: Haoyuan Wang and Sijie Li.

(IV) Data analysis and interpretation: Haoyuan Wang, Sijie Li, Tao Li, Tianyi Wang and Jiahu Lin.

(V) Manuscript writing: Haoyuan Wang.

(VI) Final approval of manuscript: All authors.

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Tables

Table1. A summary of prostate cancer bone metastases microarray datasets from different GEO datasets.

	Series	Platform	Affymetrix GeneChip	Samples
1	GSE32269	GPL96	[HG-U133A] Affymetrix Human Genome U133A Array	55
2	GSE74367	GPL15659	Agilent-016162 PEDB Whole Human Genome Microarray 4x44K [Probe Name version]	76
3	GSE77930	GPL21289	Agilent-023364 Custom Whole Human Genome CGH Microarray 2x415K [Probe Name version]	320

Table 2. A summary of hub genes.

Gene Symbol	Description	Gene Summary
CENPE	centromere protein E	GO:0099607 lateral attachment of mitotic spindle microtubules to kinetochore; GO:0099606 microtubule plus-end directed mitotic chromosome migration; GO:0007079 mitotic chromosome movement towards spindle pole
KIF2C	kinesin family member 2C	GO:0051315 attachment of mitotic spindle microtubules to kinetochore; GO:0019886 antigen processing and presentation of exogenous peptide antigen via MHC class II; GO:0030951 establishment or maintenance of microtubule cytoskeleton polarity
BUB1	BUB1 mitotic checkpoint serine/threonine kinase	GO:0007094 mitotic spindle assembly checkpoint; GO:0051754 meiotic sister chromatid cohesion, centromeric; GO:0071174 mitotic spindle checkpoint
KIF11	kinesin family member 11	GO:0046602 regulation of mitotic centrosome separation; GO:0007100 mitotic centrosome separation; GO:0051299 centrosome separation
KIF20A	kinesin family member 20A	GO:0061952 midbody abscission; GO:1902410 mitotic cytokinetic process; GO:0032506 cytokinetic process
TTK	TTK protein kinase	GO:0033316 meiotic spindle assembly checkpoint; GO:0044779 meiotic spindle checkpoint; GO:1902103 negative regulation of metaphase/anaphase transition of meiotic cell cycle

Table.3 A summary of miRNAs that regulate hub genes.

	Gene	Predicted MiR		Gene	Predicted MiR
1	CENPE	hsa-miR-3919 hsa-miR-520a-5p hsa-miR-525-5p	5	KIF20A	hsa-miR-369-3p hsa-miR-374b-5p hsa-miR-374a-5p
2	KIF2C	hsa-miR-6715a-3p hsa-miR-6715b-3p hsa-miR-6772-5p	6	TTK	hsa-miR-455-3p.1 hsa-miR-212-3p hsa-miR-132-3p
3	BUB1	hsa-miR-495-3p hsa-miR-5688 hsa-miR-3169	7	RACGAP1	hsa-miR-485-5p hsa-miR-6884-5p hsa-miR-19b-3p
4	KIF11	hsa-miR-101-3p.2 hsa-miR-374c-5p hsa-miR-655-3p			

Table.4 The genes and their effect on prostate cancer bone metastases based on univariate logistic proportional regression analysis.

GENE	OR	95% CI	P
KIF11	2.331	1.049-5.178	.038
KIF20A	0.108	0.024-0.493	.004

Table.5 The genes and their effect on prostate cancer bone metastases based on multivariate logistic proportional regression analysis.

GENE	OR	95% CI	P
KIF11	2.331	1.049-5.178	.038

Figures

Figure 1

WGCNA analysis of the genes in the merged series. (A) The cluster of patients with clinical information, red line represents patients with PCa bone metastasis. (B) The lowest power for which scale independence. (C) Repeated hierarchical clustering tree. (D) The dendrogram and heatmap of genes. (E) Interactions between modules. (F) The associations between clinic traits and the modules, and tan module is most relevant to clinical traits.

Figure 2

Gene functional enrichment analysis of the tan model genes by Metascape and GSEA. (A) Enrichment GO Cluster analysis by Metascape. (B) Enrichment KEGG Cluster analyses by Metascape. (C) Enrichment GO P-Value analyses by Metascape. (D) Enrichment KEGG P-Value analyses by Metascape. (E) Enrichment heatmap Heatmap selected GO analyses by Metascape. (F) Enrichment heatmap Heatmap Selected KEGG analyses by Metascape.

Figure 3

Differential expression analysis of the genes in the merged series. (A) Heatmap of the 877 DEGs in the tan model. (B) Volcano plot of the genes which are different expression (DEGs) between PCa bone metastasis group and primary PCa group. (C) Venn plot of common genes between DEGs and tan model genes. (D) The protein–protein interaction (PPI) network complex for the common DEGs. (E) The common hub genes identified from different algorithm. (F) The common hub genes of protein-protein interaction network.

Figure 4

Relationship to PCa bone metastasis related to common hub genes based on the CTD database.

Figure 5

Functional and pathway enrichment analysis of miRNAs which could regulate hub genes. (A) BP analysis (B) CC analysis. (C) MF analysis. (D) KEGG analysis.

Figure 6

Clinicopathological information of the hub gene. (A) Disease free survival analysis of hub genes. (B) Validation of KIF11 on a translational level using the Human Protein Atlas database.