High UBE2T mRNA expression and its prognostic significance in Ovarian cancer: a study based on data mining

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Research article

Keywords: Ovarian cancer, Ubiquitin conjugating enzyme E2 T, data mining, prognosis

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Abstract

Background

Ovarian cancer (OC) affects about 22 000 women annually in the US and ranks 5th in cancer deaths, largely due to diagnosed with advanced stage. Epithelial ovarian cancer (EOC) accounts for approximately 90% of all ovarian cancer cases. Our study was to assess the prognostic meaningful of UBE2T expression in OC dependent on data acquired from TCGA and so as to increase further knowledge into the biological pathways involved in OC pathogenesis related to UBE2T.

Methods

Information on gene expression and comparing clinical data were recognized and downloaded from TCGA. Gene set enrichment analysis (GSEA) created an arranged list of all genes s indicated by their connection with UBE2T expression.

Results

The scatter plot showed the difference of UBE2T expression between normal and tumor samples (P <0.01). So as to decide the biological interaction network of UBE2T in OC, we used to tab Network in cBioPortal and the 50 most as often altered neighbor genes of UBE2T were demonstrated utilizing Network and the most frequent alterations were HES1. The GSEA results showed that cell cycle, DNA replication, RNA degradation, some cancers, spliceosome, Huntington's disease, oxidative phosphorylation are differentially enriched in UBE2T high expression phenotype. Cumulative survive showed that dendritic cell of immune infiltrates statistically significant (P <0.05) of UBE2T in OC suggesting that dendritic cell significantly affecting the prognosis, it is worth more research and exploration.

Conclusion

Our study found that the expression of UBE2T was significantly increased in OC patients and associated with several clinical features. UBE2T may be a potentially useful prognostic molecular biomarker of bad survival in OC, while further experimental ought to be performed to demonstrate the biologic effect of UBE2T.

Background

Ovarian cancer (OC) affects near 22 000 women annually in the US and ranks 5th in cancer deaths, largely due to diagnosed with advanced stage[1]. Epithelial ovarian cancer (EOC) constitute about 90% of all ovarian cancer cases[2]. Despite recent advances in cyto-reductive surgery and chemotherapy, the 5-year survival rate of EOC patients is only 30% and the prognosis of EOC remains poor. If effective early detection is possible, the survival rate can usually be increased to 70%. The leading cause of death was by extensive peritoneal metastasis, and the specific molecular mechanism remains unclear[3]. Several

aspects effect the progression of the disease. Epigenetic and genetic factors are the most important ones among them. Mutations and the damage of the TP53 function are found in 60%-80% of the familial and sporadic cases of the disease[4]. Study reported that ET-1R/β-arr1 axis enables cancer cells to involve several integrated signaling in OC and may be a novel therapeutic approach[5]. Pan et al reported that LINC00339 regulated ovarian cancer cell migration, proliferation and invasion by targeting miR-148a-3p/ROCK1 axes. Moreover, a recent study found Rab23 is highly expressed in ovarian cancer tissues and related to advanced stage, and shortened overall survival time of ovarian cancer patients[7]. Similarly, Wu et al found high expression of SCNN1A was related to poor overall survival and progression-free survival in OC patients[8]. Due to lacking specific and sensitive early biomarkers, a high possibility of metastasis and drug resistance is considered to make contributions the high mortality of OC. In this way, it is necessary for recognizing the more sensitive and specific novel target molecules for developing effective diagnosis and treatment strategies of OC.

Posttranscriptional modifications are vital in the initiation and the progression of tumors. Ubiquitin conjugating enzyme E2 T (UBE2T; otherwise called FANCT; PIG50; HSPC150), is a member of the ubiquitin-proteasome family and encoded a protein catalyzes the covalent attachment of ubiquitin to protein substrates. It was initially reported in Fanconi anemia and is important to DNA damage repair[9]. UBE2T participates in main cellular processes such as signal transduction, cell cycle control and tumorigenesis via triggering the degradation of relevant substrates[10]. Studies reported that UBE2T is amplified in a wide variety of tumors. Ueki et al[11] implied a key role of UBE2T in the progression of breast cancer through the regulation and the interaction with the BRCA1/BARD1 complex. Hu et al[12] demonstrated that UBE2T might promote the development and progression of nasopharyngeal carcinoma by activating the AKT/GSK3β/β-catenin pathway. Gong et al[13] reported that the knockdown of UBE2T significantly diminished bladder cancer cell proliferation and colony formation. Liu et al[14] found that miR-543/UBE2T/p53 axis might represent a new significant potential therapeutic target for hepatocellular carcinoma intervention. Luo et al[15] reported that UBE2T facilitate the tumor invasion and metastasis in gastric cancer via triggered the epithelial mesenchymal transition process. In our study, we have assessed the expression of UBE2T in OC dependent on data acquired from online databases and so as to increase further knowledge into the biological pathways involved in OC pathogenesis related UBE2T.

Methods

TCGA and GSEA analysis

Information on gene expression were recognized and downloaded from Genotype Tissue Expression (GTEx) projects and The Cancer Genome Atlas (TCGA) via UCSC database (https://genome.ucsc.edu)[15]. Boxplots were utilized to envision expression differences for discrete variables. Gene set enrichment analysis (GSEA) created an arranged list of all genes s indicated by their connection with UBE2T expression. Then samples were divided into high- and low-UBE2T groups as training set to distinguish the potential function and elucidate the significant survival difference utilizing GSEA. Annotated gene sets

c2.cp.kegg.v6.0.symbols.gmt was selected as the reference gene sets, which includes terms with FDR < 0.05. Gene set permutations were executed multiple times for every examination. The expression degree of UBE2T was applied as a phenotype label. The normalized enrichment score (NES) and nominal P value had been used to kind the pathways enriched in every phenotype.

UALCAN Dataset and Kaplan-Meier plotter

UALCAN[16] is an intelligence and user-friendly web asset for discovering, analyzing and integrating cancer transcriptome data and in-depth analyses of TCGA gene expression data. The prognostic meaning of mRNA expression of UBE2T in OC was assessed by using Kaplan-Meier plotter[17], in which data about gene expression with survival of patients in 21 cancer types. In Kaplan-Meier plotter, cancer patient samples were split into low and high expression group according to median values of mRNA expression and assessed by K-M survival plot.

CBioPortal analysis and immune infiltrates analysis

cBioPortal[18] is an open access asset that visualizes, analyzes and downloads large-scale cancer genomics datasets. The portal currently contains 245 cancer studies. We used c-BioPortal to analyze UBE2T changes in TCGA OV samples and showed an overview of the genetic changes in each test in UBE2T. We constructed a UBI2T tag biointeraction network. TIMER[19] is a useful asset for systematically studying the immune infiltration of various malignancies. The abundance of six immune infiltrates (CD8 + T cells/B cells/CD4 + T cells/macrophages/neutrophils/dendritic cells) was assessed by our statistical methods and pathological estimation methods have been used. It was evaluated.

TargetScan analysis

TargetScan[20] is a web interface for predicting miRNA biological targets. TargetScanHuman believes that matching to human 3'UTR and its orthologs is characterized by a UCSC genome-wide alignment. FunRich[21] is a programming tool designed to process a variety of gene/protein datasets that are not related to organisms and are used for functional enrichment and interaction of genes and proteins. Network analysis. Currently, TargetScan is used to study differentially expressed miRNAs associated with UBE2T, and then we use the Funrich tool for miRNA enrichment analysis, involving biological processes, cellular components, molecular functions, and biological pathways.

Results

Association with UBE2T expression and clinicopathologic factors

The scatter plot showed the difference of UBE2T expression between normal and tumor samples (P < 0.01), Fig. 1A. We next used UALCAN to explore the relationship of expression of UBE2T and clinical factors. In age subgroup (normal-vs-age (21-40yrs), normal-vs-age (41-60yrs), normal-vs-age (61-80yrs) and normal-vs-age (81-100yrs)) analysis the transcription level of UBE2T was essentially higher in OC

patients than normal individuals; race subgroup and tumor grade subgroup analysis the UBE2T was also significantly higher in OC patients Fig. 1B-1E.

GSEA recognizes UBE2T related signaling pathway

In order to recognize signaling pathways which might be differentially initiated in OC, we led GSEA analysis among low and high UBE2T expression data sets (FDR P < 0.05, NOM P < 0.05). We chose the most significantly enriched signaling pathways dependent on normalized enrichment score (NES) Table 1. The results show that cell cycle, DNA replication, RNA degradation, some cancers, spliceosome, Huntington's disease, oxidative phosphorylation are differentially enriched in UBE2T high expression phenotype Fig. 2.

Gene set name	SIZE	NES	NOM p-val	FDR q-val
KEGG_CELL_CYCLE	123	2.32	0.000	0.000
KEGG_DNA_REPLICATION	36	2.32	0.000	0.000
KEGG_RNA_DEGRADATION	59	2.41	0.000	0.000
KEGG_OXIDATIVE_PHOSPHORYLATION	131	2.16	0.000	0.002
KEGG_HUNTINGTONS_DISEASE	180	2.19	0.000	0.001
KEGG_SPLICEOSOME	127	2.38	0.000	0.000
NES: normalized enrichment score; NOM: nominal; FDR: false discovery rate. Gene sets with NOM p-val 0.05 and FDR q-val <0.25 are considered as significant.				

Table 1
Gene sets enriched in phenotype high

Survival and cBioPortal results

Overall survival (OS), progression-free survival (PFS) and post-progression survival (PPS) analysis demonstrated that OC with UBE2T -high had a more terrible prognosis than that with UBE2T -low (P < 0.05) Fig. 3. So as to decide the biological interaction network of UBE2T in OC, we used to tab Network in cBioPortal and the 50 most as often altered neighbor genes of UBE2T were demonstrated utilizing Network and the most frequent alterations were HES1 (14.2%) (Fig. 4 and Table 2).

Gene Symbol	Amplification	Homozygous Deletion	Mutation	Total Alteration
HES1	13.6	0.3	0.3	14.2
RFC4	13.3	0	0	13.3
FAAP24	7.9	0	0	7.9
UBE3C	6.3	0.3	0	6.6
UBE2Q1	4.7	0	0	4.7

Table 2
The type and frequency of *UBE2T* neighbor gene alterations in OC (cBioPortal).

Immune infiltrates and miRNAs in correlation with UBE2T in OC

OC expression of UBE2T immune infiltrates (B cells, CD4 + T cells, CD8 + T cells, neutrophils, macrophages, and dendritic cells) correlation between the abundance of statistical significance ($P < 0.05$, Fig. 5A). Cumulative survival showed that UBC2T immunosuppressive dendritic cells in OC were statistically significant ($P < 0.05$), indicating that dendritic cells significantly affected prognosis and warrant further study and exploration (Fig. 5B). A box plot was introduced to demonstrate the distribution of each immunization subgroup in each copy number state with UBE2T in OC. According to the cumulative weighted context + + score, the top three of the 1169 miRNA families associated with the gene UBE2T in OC are hsa-miR-5580-3p, hsa-miR-3652 and hsa-miR-4430. Figure 6A shows conserved sites of the widely conserved miRNA family in vertebrates. To examine the function of the identified 1169 miRNAs, bioconcentration was performed by the Funrich database. Biological processes are significantly rich in nucleobase regulation, signal transduction, cellular communication, transport, cell growth, and regulation of cellular tissue and biogenesis. Cellular components are mainly enriched in the nucleus, cytoplasm, Golgi apparatus, endosomes, lysosomes and early endosomes. Molecular functions are mainly enhanced by transcription factor activity, transcriptional regulatory activity, protein serine, GTPase activity and ubiquitin-specific protease activity; biological pathways are abundant, including Glypican pathway, proteoglycan syndecan-mediated signaling events, VEGF and VEGFR signals Network, TRAIL signaling pathway, sphingosine 1-phosphate (S1P) pathway and ErbB signaling pathway Fig. 6B-6E.

Discussion

In this study, we conducted a comprehensive and detailed assessment of UBE2T expression in ovarian cancer based on online database and to explore its association with clinicopathologic characteristics, survival, function, immune infiltrates and expression difference. Knowing whether a more highly-expression biomarkers in tumor consists of a right away link to ovarian cancer help us understand the mechanistic clarification for observed clinical survival patterns. In our outcomes, UBE2T significantly

expression between normal and tumor samples indicated that UBE2T may plays an important role in regulate cancer progression.

UBE2T as for a member of E2 the family in the ubiquitin-proteasome pathway, a complex protein degradation system that participated in extensive biological processes, including signal transduction, tumorigenesis, cell proliferation, differentiation and cell cycle control. Numerous studies identified that its overexpression results in a variety of tumorigenesis such as osteosarcoma, diffuse large B-cell lymphoma and malignant pleural mesothelioma[22 – 24]. Until now, the expression of UBE2T and its potential prognostic effect on OC has not yet been investigated. Our outcomes showed that OC with UBE2T -high had a more terrible prognosis than that with UBE2T -low ($P < 0.05$) in OS, PFS and PPS. Moreover, we used UALCAN database to further analysis of multiple clinic pathological features of OC samples and all indicated high transcription of UBE2T. In order to recognize signaling pathways that are differentially in OC, we then performed GSEA analysis among low and high UBE2T expression data sets. The results show that cell cycle, DNA replication, RNA degradation, some cancers, spliceosome, Huntington's disease, oxidative phosphorylation are differentially enriched in UBE2T high expression phenotype. UBE2T may affect cell cycle, DNA replication, RNA degradation then regulates the occurrence and development of cancer cells. Hao et al[25] was first to investigate the expression of UBE2T mRNA in normal human tissues and 8 lung cancer cell lines and found UBE2T was significantly upregulated in lung cancer tissue and cell lines, suggesting involvement of UBE2T in the malignant cell phenotype. The ubiquitin-proteasome system exerts a crucial role in extensive biological processes, and UBE2T, its crucial member, may affect tumorigenesis and cell cycle. Studies on the function of UBE2T in cancer will undoubtedly provide new insights regarding the role UBE2T in both cell cycle regulation and tumorigenesis.

In order to decide the biological interaction network of UBE2T in OC, we applied to tab Network in cBioPortal and the 50 most as often altered neighbor genes of CENPM and the most frequent alterations were HES1. Hes family bHLH transcription factor 1 (HES1) belongs to the basic helix-loop-helix family of transcription factors. A recent study found that Hes1 expression oscillates and drives cyclic expression of the proneural gene Ascl1, which activates cell proliferation in active neural stem cells[26]. Study also found that indicating that the Notch1/Hes1/MMPs pathway ST6Gal-can mediate the invasiveness and tumorigenicity of non-small cell lung cancer (NSCLC) cells in vitro and in vivo[27]. Huang et al[28] demonstrated that HES1 is a specific downstream gene of NOTCH1 and that it contributes to salivary adenoid cystic carcinoma proliferation, apoptosis and metastasis. In addition, Islam et al reported[29] that cisplatin/eugenol sequential combination could be of great therapeutic value for ovarian cancer patients through targeting the Notch-Hes1 pathway and the consequent elimination of the resistant cancer stem cells. So, our study may provide information for HES1 on replication forks study in OC patients.

Until now, there was no related study try to explore the connection of immune infiltrates and UBE2T, we first study the immune infiltrates and miRNAs in correlation with UBE2T in OC. Correlation between UBE2T in OC expression and abundance of immune infiltrates was statistically significant and the

cumulative survive showed that dendritic cell of immune infiltrates statistically significant ($P < 0.05$) of UBE2T in OC indicating that dendritic cell significantly affecting the prognosis, it is worth further research and exploration. We finally study the miRNAs that correlation with UBE2T in OC. The top 3 among 1169 miRNAs family was hsa-miR-5580-3p, hsa-miR-3652 and hsa-miR-4430 that related to gene UBE2T in OC. Study reported miR-3652 association with oral squamous cell carcinoma prognosis and miR-4430 related to breast cancer cells prognosis[30,31]. In order to explore the function of the identified 1169 miRNAs, biological enrichment was performed through Funrich database. Biological pathway enriched in glypican pathway, proteoglycan syndecan-mediated signaling events, VEGF and VEGFR signaling network, TRAIL signaling pathway, sphingosine 1-phosphate (S1P) pathway and ErbB signaling pathway. Thus, UBE2T may help us understand the protein disease pathogenesis and progression in future study. Our study found that the expression of UBE2T was significantly increased in OC patients and associated with several clinical features. UBE2T may be a potentially useful prognostic molecular biomarker of bad survival in OC, while further experimental ought to be performed to demonstrate the biologic effect of UBE2T.

Abbreviations

OC: Ovarian cancer; UBE2T: Ubiquitin conjugating enzyme E2 T; TCGA: cancer genome atlas; OS: over survival.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent to public

Not applicable.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

W.Z.H. designed and analyzed the research study; W.Z.H. wrote and revised the manuscript, W.Z.H. collected the data and all authors contributed to and approved the final version of manuscript.

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Not applicable

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Figures

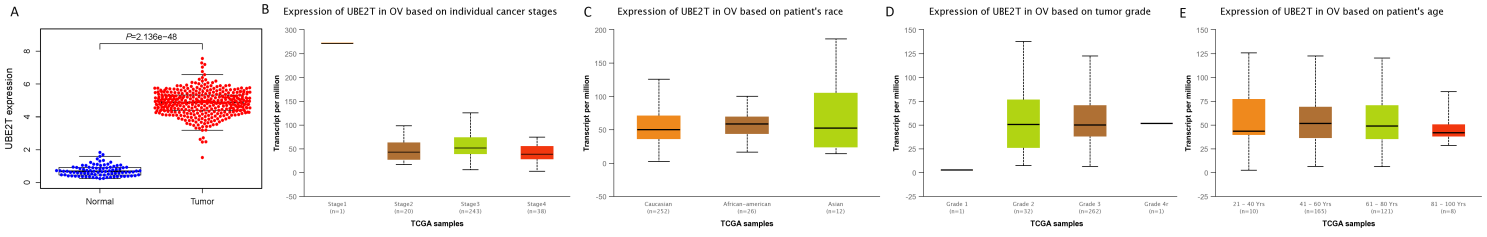

Figure 1

The scatter plot showed the difference of UBE2T expression between normal and tumor samples (P<0.01), Fig. 1A. We next used UALCAN to explore the relationship of expression of UBE2T and clinical factors. In age subgroup (normal-vs-age (21-40yrs), normal-vs-age (41-60yrs), normal-vs-age (61-80yrs) and normal-vs-age (81-100yrs)) analysis the transcription level of UBE2T was essentially higher in OC patients than normal individuals; race subgroup and tumor grade subgroup analysis the UBE2T was also significantly higher in OC patients Fig. 1B-1E.

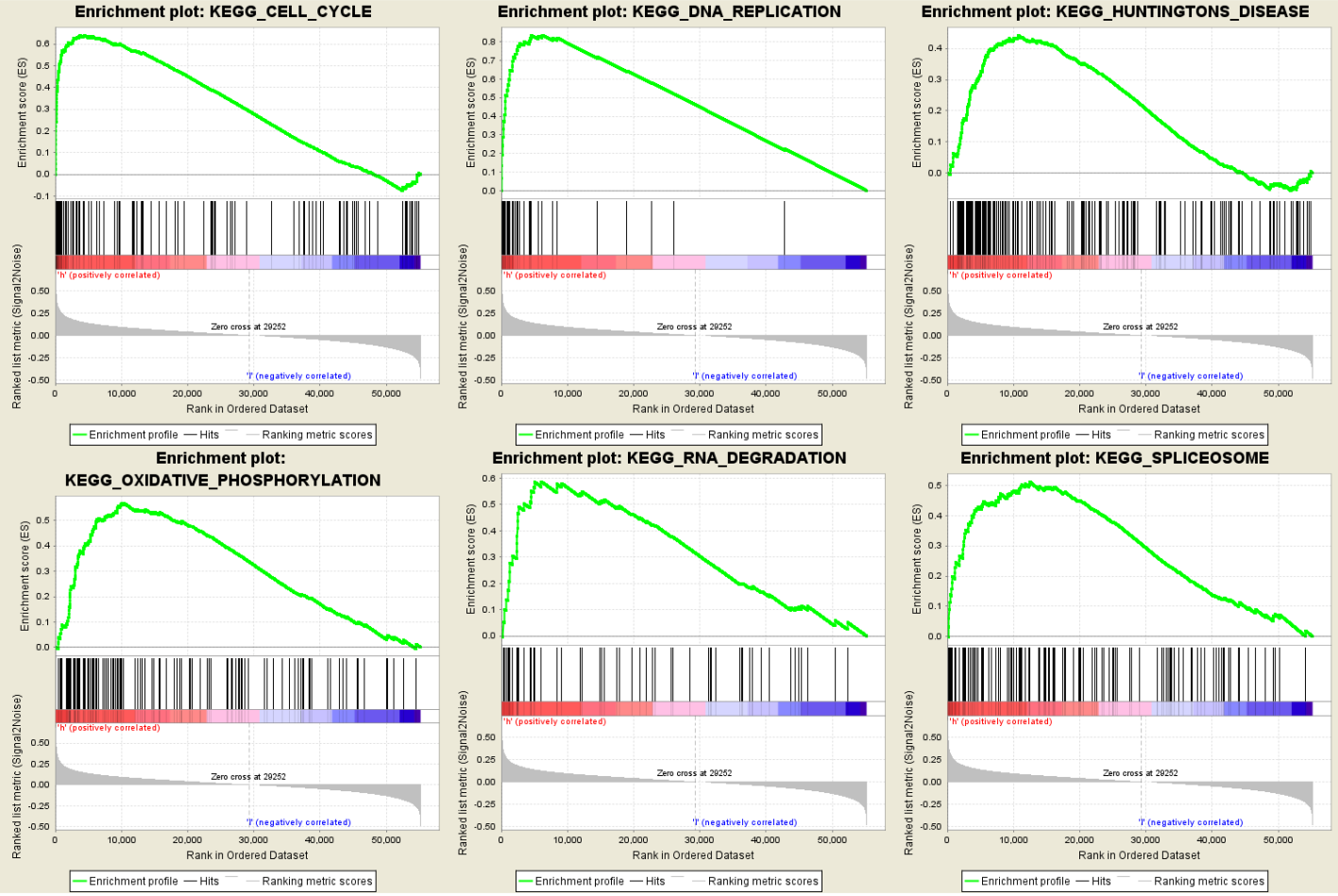

Figure 2

The results show that cell cycle, DNA replication, RNA degradation, some cancers, spliceosome, Huntington's disease, oxidative phosphorylation are differentially enriched in UBE2T high expression phenotype

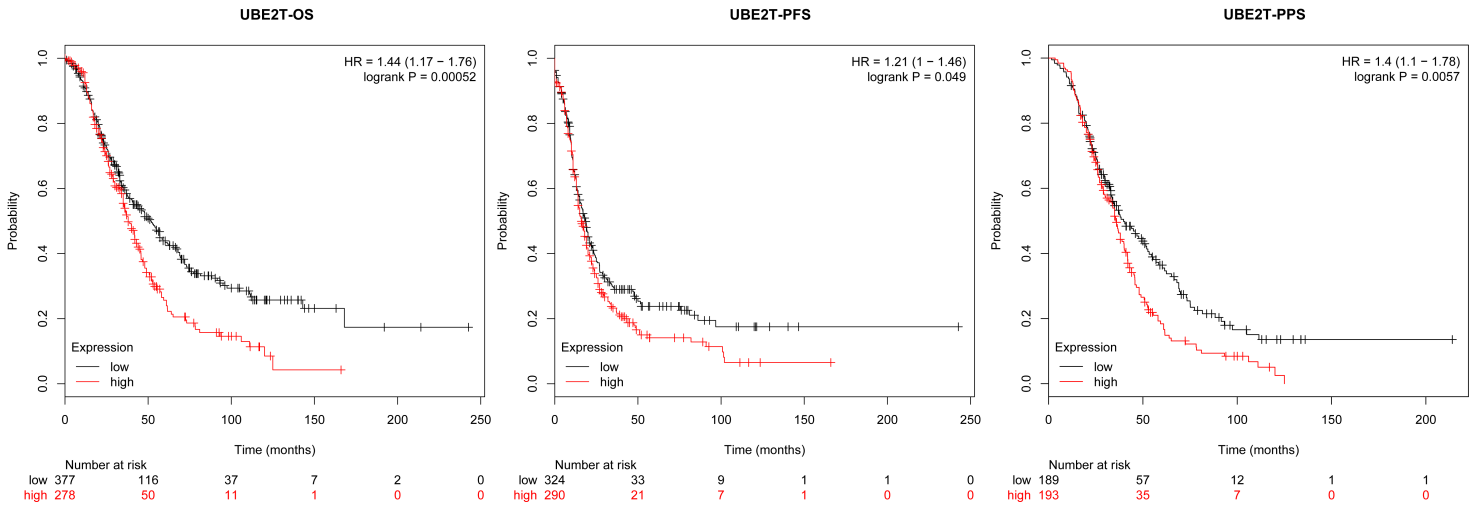

Figure 3

Overall survival (OS), progression-free survival (PFS) and post-progression survival (PPS) analysis demonstrated that OC with UBE2T -high had a more terrible prognosis than that with UBE2T -low (P<0.05)

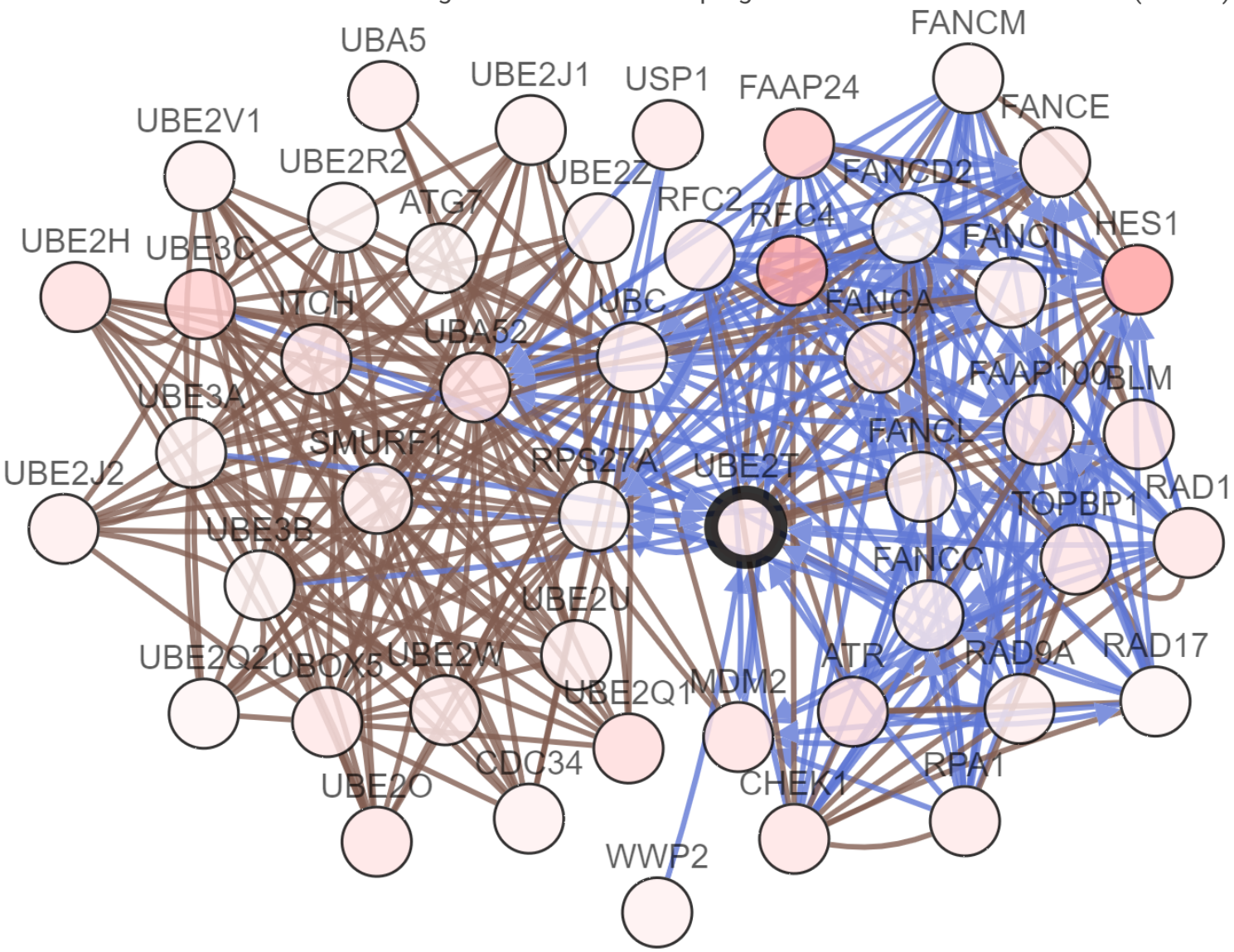

Figure 4

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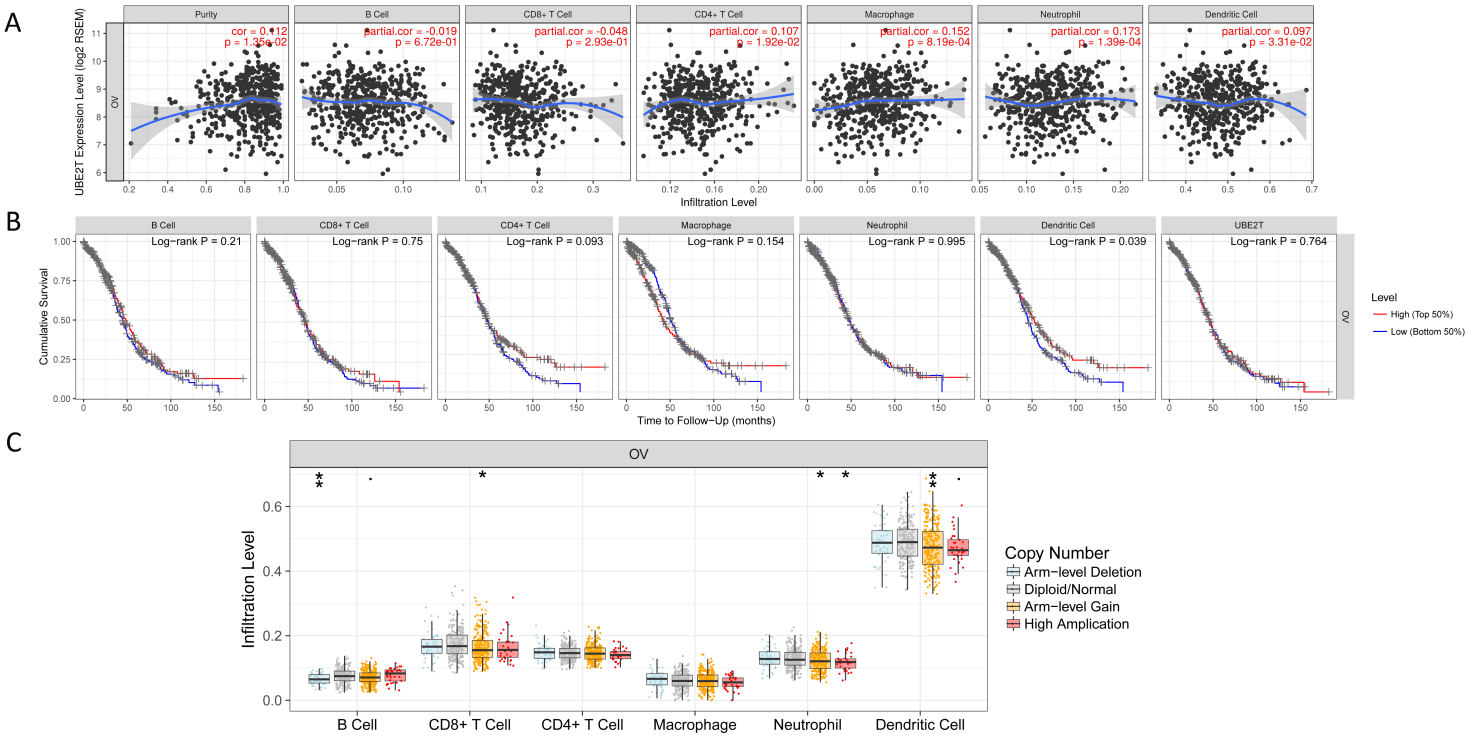

Figure 5

OC expression of UBE2T immune infiltrates (B cells, CD4 + T cells, CD8 + T cells, neutrophils, macrophages, and dendritic cells) correlation between the abundance of statistical significance (P <0.05, Fig. 5A). Cumulative survival showed that UBC2T immunosuppressive dendritic cells in OC were statistically significant (P<0.05), indicating that dendritic cells significantly affected prognosis and warrant further study and exploration (Fig. 5B).

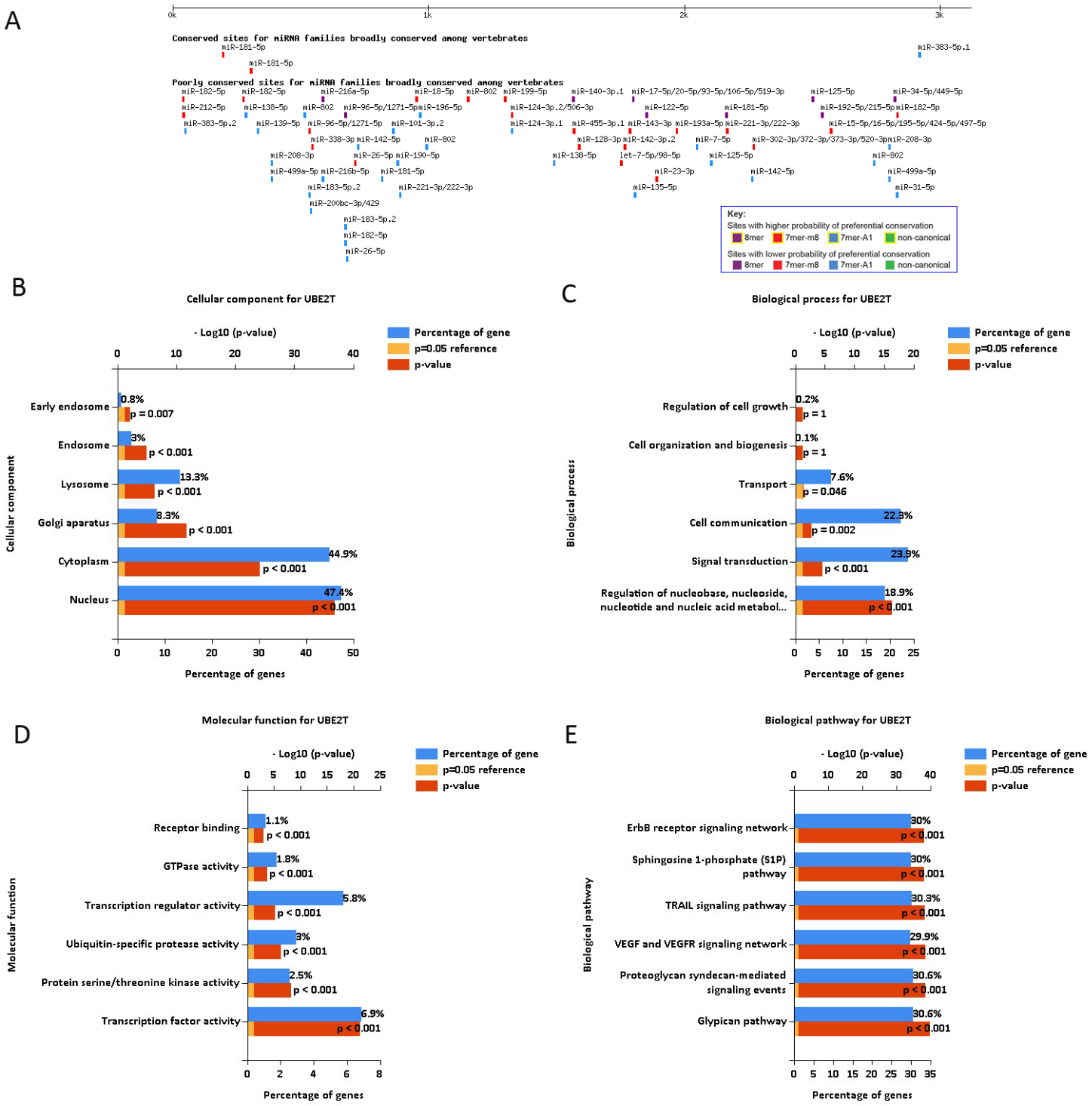

Figure 6

A box plot was introduced to demonstrate the distribution of each immunization subgroup in each copy number state with UBE2T in OC. According to the cumulative weighted context ++ score, the top three of the 1169 miRNA families associated with the gene UBE2T in OC are hsa-miR-5580-3p, hsa-miR-3652 and hsa-miR-4430. Fig. 6A shows conserved sites of the widely conserved miRNA family in vertebrates. To examine the function of the identified 1169 miRNAs, bioconcentration was performed by the Funrich

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