Fatty acid-binding protein 5 predicts poor prognosis in patients with uveal melanoma

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Abstract. Fatty acid-binding protein 5 (*FABP5*), which participates in mediating the biological properties of tumor cells, has been recognized in several neoplasms. The present study aims to investigate *FABP5* transcriptional expression profiles, reveal its underlying biological interaction networks and define its prognostic value in uveal melanoma (UVM). A total of 80 patients with UVM and their RNA-sequence data, available from The Cancer Genome Atlas (TCGA) database, was analyzed. A differential transcriptional expression profile was obtained from TCGA and the Oncomine databases. The survival benefits were analyzed using the Kaplan-Meier method and log-rank test. The correlation between *FABP5* expression and immune infiltration level was analyzed using the Tumor Immune Estimation Resource database. Functional enrichment analyses using Gene Ontology, Kyoto Encyclopedia of Genes and Genomes, and signaling hallmarks were utilized to describe the biological process, molecular functions, cellular component and significantly involved pathways. The elevated transcriptional expression of *FABP5* was significantly associated with shorter overall survival (OS) and worse progression-free survival (PFS) times in patients with UVM (P<0.001). Moreover, *FABP5* expression was significantly and positively correlated with tumor purity and $CD8^+$ T cells and was negatively correlated with the infiltrating levels of $CD4^+$ T cells and neutrophils. Gene Set Enrichment Analysis was performed to obtain 100 significantly associated genes of *FABP5* and *FABP5* was found to be critical in several hallmark pathways, including allograft rejection, complement, interleukin-6/Janus kinase-STAT3 signaling, interferon γ response, inflammatory response and tumor necrosis factor α signaling via NFκB. The present study is the first to demonstrate that *FABP5* expression was positively associated with progression-associated clinicopathological factors and poor prognosis in UVM, which suggests its likely function as an oncogene and prognostic marker in patients with UVM.

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Abbreviations: UVM, uveal melanoma; FABP5, fatty acid-binding protein 5; TCGA, The Cancer Genome Atlas; PFS, progression-free survival; OS, overall survival; GO, Gene Ontology; BP, biological processes; CC, cellular components; MF, molecular function; KEGG, Kyoto Encyclopedia of Genes and Genomes; PPI, protein-protein interaction; GSEA, Gene Set Enrichment Analysis

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Key words: uveal melanoma, fatty acid-binding protein 5, biological markers, prognosis, mRNA

Introduction

Uveal melanoma (UVM) is the cause of ~85% of all ocular melanomas and is the most common primary intraocular malignancy in adults (1). The average annual incidence of UVM in the US is 5.1 per million between 1973 and 2012 (95% CI, 4.2-6.1) (2). Approximately 50% of patients with UVM develop metastatic disease (3), with the liver being the most common initial site of metastasis. Patients with metastatic disease are rarely candidates for curative surgery and generally have a poor prognosis; death often occurs within a few months of the development of metastases (4,5). Although the incidence rate of UVM is known to be influenced by a number of parameters, including demographic, geographic and, to a lesser extent, hereditary factors, little is known about the underlying mechanisms responsible for its initiation, progression or biological heterogeneity. Consequently, there is an urgent need to increase the understanding of the molecular and cellular biology of UVM, which will aid in the development not only of novel prognostic biomarkers but also of individualized treatment regimens.

Fatty acid-binding proteins (FABPs) are a protein family (6) that bind to hydrophobic lipids, including various retinoids and long-chain fatty acids and are involved in lipid metabolism (7) by affecting lipid transport, storage, membrane incorporation and transcriptional regulation (8,9). The *FABP5* isoform is an intracellular lipid-binding protein that is highly expressed in macrophages and adipocytes (10). *FABP5* is transcriptionally

regulated by a number of cytokines and signaling pathways, including the phosphoinositide 3-kinase (PI3K)/AKT pathway and the transcription factors peroxisome proliferator-activated receptor (PPAR) β/δ and nuclear factor κ light chain enhancer of activated B cells (NFκB) (11-13). Notably, *FABP5* was over-expressed in several tumor types and its expression level was associated with the growth and metastasis of several cancer types, including prostate cancer, intrahepatic cholangiocarcinoma, colorectal cancer and cervical cancer (7,8,12,14,15).

An understanding of the regulation and function of *FABP5* in normal organ development and disease progression may identify novel targets for UVM treatment. To investigate the transcriptional expression of *FABP5* and define its prognostic value in patients with UVM, the present study focused on analyzing the gene expression profiles, revealing the underlying biological interaction networks and assessing their prognostic value. It is postulated that the potential oncogenic activity of *FABP5* correlates with poor prognosis and might reveal its potential therapeutic targets and the molecular pathogenesis of UVM.

Materials and methods

Patients and transcriptional expression profile. RNA-sequence data, from The Cancer Genome Atlas (TCGA) database (16), including 80 patients with UVM were downloaded and analyzed. The gene expression profile was detected experimentally using the Illumina HiSeq-2000 RNA Sequencing platform by the University of North Carolina TCGA genome characterization center. The X-tile software (version 3.6.1) was used to determine the cut-off value of mRNA expression of *FABP5* by assessing the biological relationships between *FABP5* mRNA expression levels and the outcome of UVM patients (17). The differential transcriptional expression levels of *FABP5* between patients with metastatic and non-metastatic UVM, from the GSE22138 dataset, was acquired from Oncomine database (18).

Oncomine database. The transcriptional expression profiles of *FABP5* in patients with UVM were publicly available from the Oncomine online database (http://www.oncomine.com), which was used to illustrate the differential expression in patients with metastatic and non-metastatic UVM (19). The expression of *FABP5* profiles from the Oncomine database was obtained based on the following criteria: i) 'Gene: *FABP5*'; ii) 'Cancer Type: Uveal Melanoma'; iii) 'Data Type: mRNA'; iv) Threshold Setting Condition (P<0.0001; fold change, >2; and gene rank, top 10%); and v) Group by 'Metastatic Event Status'.

Statistical analysis. The phenotype and expression profiles of *FABP5* in 80 patients with UVM from TCGA and Oncomine databases were analyzed and presented. The transcriptional expression levels of *FABP5* in UVM and their association with clinicopathological parameters (age of the patients, tumor histology and individual cancer stages), obtained from TCGA, were analyzed and compared among different groups visually using a χ^2 test. The differential transcriptional expression levels of *FABP5* between patients with metastatic and non-metastatic UVM, from the GSE22138 dataset acquired from Oncomine database (18), was analyzed using Student's t-test. Survival comparison between distinct mRNA expression levels groups of *FABP5* was analyzed in patients with UVM from TCGA database. Overall survival (OS), which was evaluated from the date of first therapy to the date of death or last follow-up, was the primary end point. The secondary end point was progression-free survival (PFS), which was the duration between the onset of curative treatment and the date of progression or second-line treatment or death, whichever occurred first. The follow-up duration was evaluated using the Kaplan-Meier method with log-rank test and 95% CI of the separate curves. Partial Spearman's correlation and statistical significance were calculated for the correlation analysis between *FABP5* expression levels and immune infiltration levels. The hypothetical tests were bilateral and P<0.05 was considered to indicate a statistically significant difference. The receiver operating characteristic curve (ROC) was constructed by predicting the probability of a diagnosis being of high or low integrated score of significant hub gene expression. The area under curve (AUC) analysis was used to assess the diagnostic ability.

Tumor immune estimation resource (TIMER) database analysis. The correlation between *FABP5* expression and the abundance of immune infiltrates in UVM was analyzed using TIMER (cistrome.shinyapps.io/timer/), which is an integrated resource for the scientific analysis of immune infiltrates across multiple cancer types (20). TIMER applies a previously published deconvolution statistical method to infer several tumor-infiltrating immune cells from gene expression profiles (21). The TIMER database includes 10,897 samples across 32 cancer types from TCGA, enabling the evaluation of the abundance of immune infiltrates. The correlation between *FABP5* expression and the various immune infiltrates, including $CD8^+$ T cells, $CD4^+$ T cells and neutrophils, were analyzed via gene modules. The gene expression levels against tumor purity are displayed on the left-most panel (22). Tumor purity is the proportion of cancer cells in the admixture. Genes highly expressed in the microenvironment are expected to have negative associations with tumor purity, whereas genes highly expressed in the tumor cells are expected to have positive associations with tumor purity.

Protein-protein interaction (PPI) network construction and module analysis. PPIs are physical contacts of high specificity that are established between proteins, as a result of biochemical events steered by electrostatic forces. The PPI network is essential in understanding cell physiology in normal and disease states and for drug development. The Search Tool for the Retrieval of Interacting Genes (http://string-db.org; version 10.0) online database was used to predict the PPI network of co-regulated hub genes and for analyzing the functional interactions between proteins (23). An interaction with a combined score of >0.4 was regarded as statistically significant.

In order to detect the potential functions, the Gene Ontology (GO) biological process (BP), cellular component (CC), molecular function (MF) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses of hub genes in this module were analyzed using the Database for Annotation, Visualization and Integrated Discovery (http://david.ncifcrf.gov;

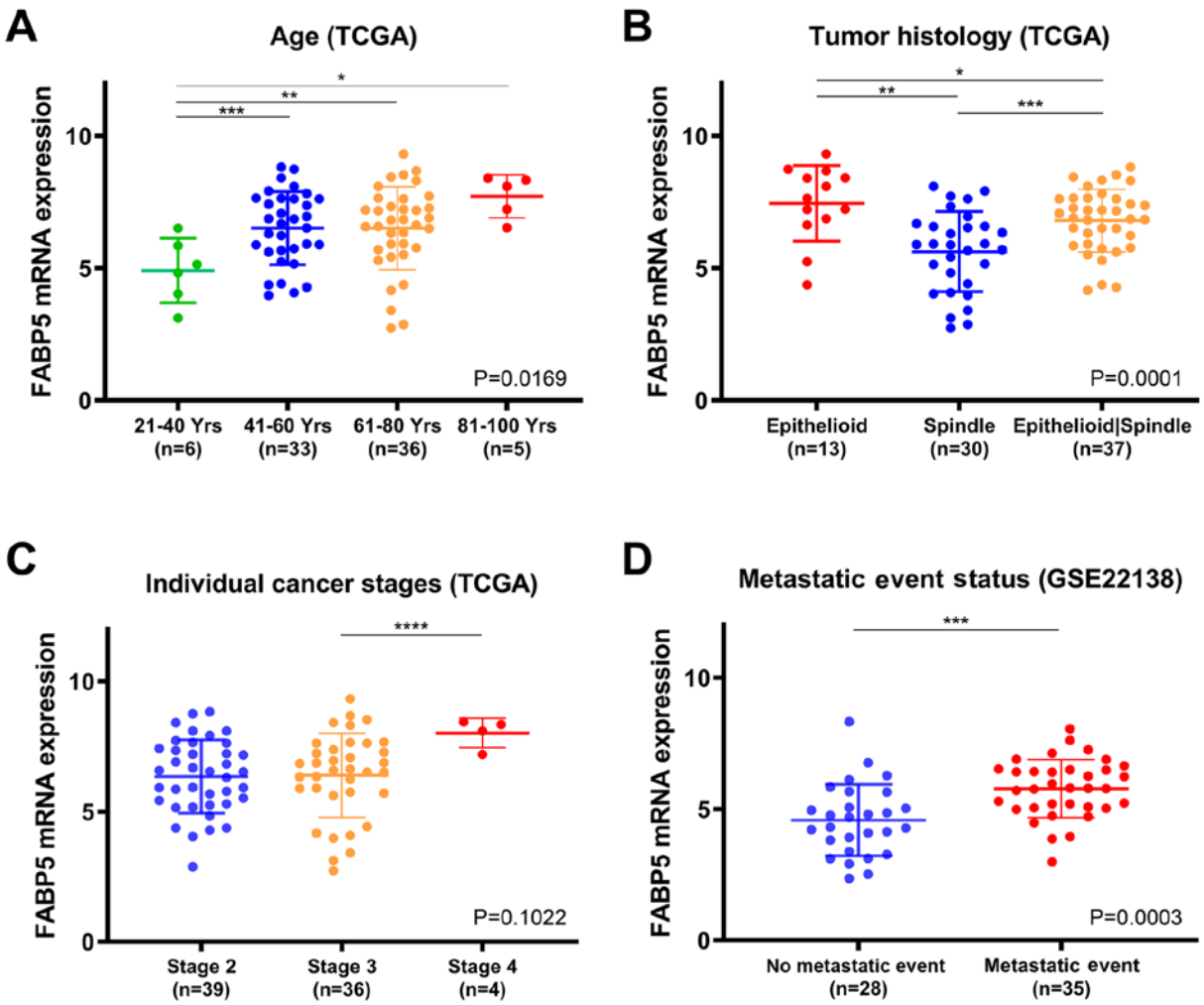

Figure 1. Transcriptional expression of *FABP5* was significantly associated with clinicopathological parameters in patients with UVM. (A and B) Transcriptional expression of *FABP5* in UVM (data from TCGA) was significantly associated with the age of the patient (P=0.0169) and tumor histology (P=0.0001). (C) Transcriptional expression of *FABP5* in UVM (data from TCGA) was not significantly associated with individual cancer stages (P=0.1022). However, the highest mRNA expression of *FABP5* was found in stage 4, which was significantly higher compared with that in stage 3. (D) Transcriptional expression of *FABP5* in UVM (data from GSE22138) was significantly higher in the metastatic group (P=0.0003). *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. *FABP5*, fatty acid-binding protein 5; UVM, uveal melanoma; TCGA, The Cancer Genome Atlas.

version 6.8) online tool (24) and subsequently visualized using a bubble chart. P<0.05 was considered to indicate a statistically significant difference.

Hierarchical partitioning was performed on the transcriptional expression profiles of eleven hub genes using a heat map. The color gradients illustrate high (blue) or low (yellow) expression levels.

Data processing of gene set enrichment analysis (GSEA). GSEA was used to determine whether the differential expression of *FABP5* was associated with a particular biological process or molecular function. TCGA database was implemented with the GSEA method using the Category version 3.0 package (25). Student's-t-test was performed for every separate analysis in consistent pathways and the mean of the differentially expressed genes was calculated. A total of 1,000 permutation tests were used to identify pathways with significant changes. The adjusted P-values (adj. P) with Benjamini and Hochberg (BH) false discovery rate (FDR) method by default were utilized to correct the occurrence of false positive results (25). The significantly associated genes were defined with an adj. P<0.01 and FDR<0.25. Statistical analysis and graphical plotting were conducted using the R software (version 3.3.2).

Results

Transcriptional expression of FABP5 in UVM based on clinicopathological parameters. As illustrated in Fig. 1, the transcriptional expression profiles of *FABP5* from the RNA-sequence data from TCGA database and the GSE22138 dataset were analyzed. The transcriptional expression of *FABP5* in UVM was significantly associated with the age of the patient (P=0.0169). The lowest mRNA expression of *FABP5* was detected in the 21-40 year age group. The transcriptional expression levels of *FABP5* was found to be higher in the 81-100 (*P<0.05), the 61-80 (**P<0.01) and the 41-60 (***P<0.001) age groups compared with that in the 21-40 age group (Fig. 1A). In addition, the transcriptional expression levels of *FABP5* in UVM was significantly associated with

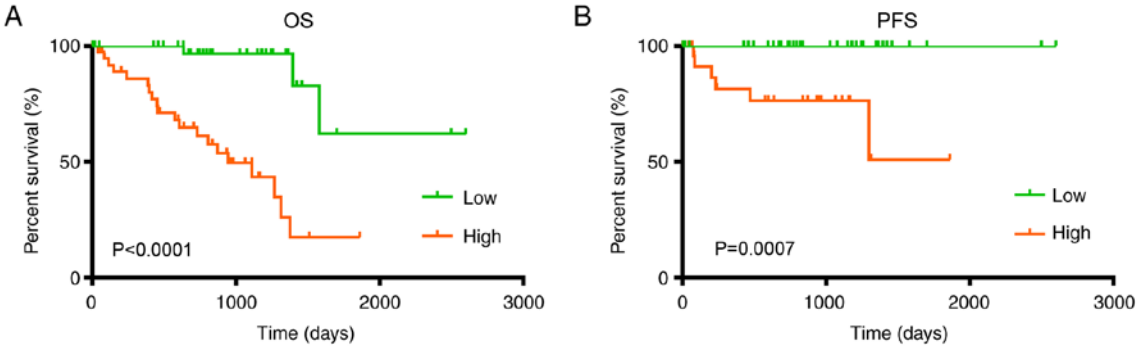

Figure 2. Kaplan-Meier survival analyses of OS and PFS in patients with UVM with differential *FABP5* expression groups. Compared with low mRNA expression, high *FABP5* expression was significantly associated with poor (A) OS (P<0.0001) and (B) PFS (P=0.0007) times. *FABP5*, fatty acid-binding protein 5; UVM, uveal melanoma; OS overall survival; PFS, progression-free survival.

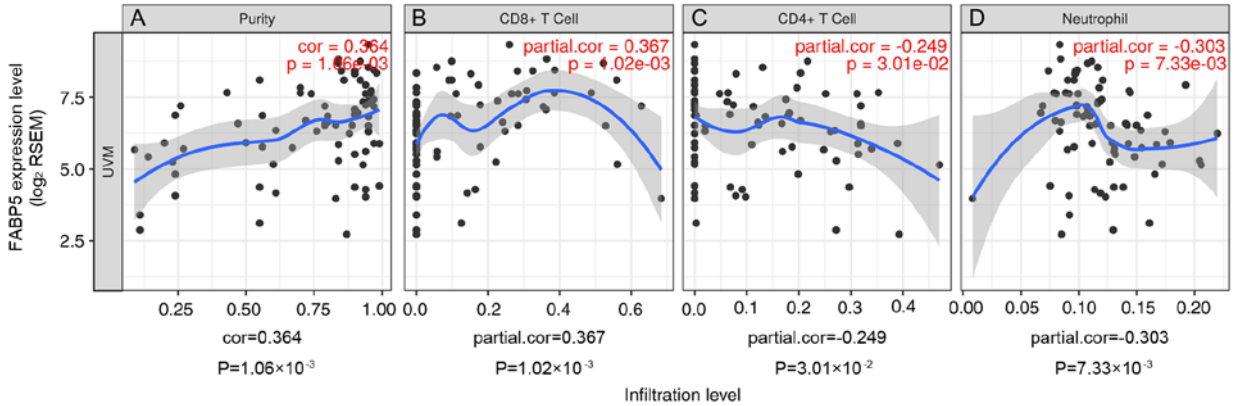

Figure 3. Correlation between *FABP5* expression and immune infiltration level in UVM. *FABP5* expression is significantly and positively correlated with tumor purity (A) and $CD8^+$ T cells (B), whereas significantly and negatively correlated with infiltrating levels of $CD4^+$ T cells (C) and neutrophils (D) (n=80). *FABP5*, fatty acid-binding protein 5; UVM, uveal melanoma; partial.cor, purity-corrected partial Spearman's correlation; RSEM, RNA-Seq by expectation-maximization.

tumor histology (P=0.0001). The highest mRNA expression levels of *FABP5* was detected in epithelioid UVM, whereas the lowest level was found in spindle cell UVM. The transcriptional expression levesl of *FABP5* was found to be higher in the epithelioid UVM compared with that in the mixed cell UVM (*P<0.05) and spindle cell UVM groups (**P<0.01), and higher in the mixed cell UVM compared with that in the spindle cell UVM (***P<0.001) group (Fig. 1B). The transcriptional expression of *FABP5* in UVM was not significantly associated with individual cancer stages (P=0.1022; Fig. 1C). However, patients who were in more advanced stages tended to express higher mRNA expression levels of *FABP5*. The highest mRNA expression of *FABP5* was found in stage 4, which was significantly higher compared with that in stage 3 (****P<0.0001). The transcriptional expression of *FABP5* in UVM was significantly associated with metastatic event status in GSE22138 (P=0.0003). A higher level of *FABP5* mRNA expression levels were found in patients with a metastatic event (Fig. 1D). The baseline clinicopathological characteristics, according to *FABP5* expression status, are shown in Table SI.

Survival outcomes of the 80 UVM patients from TCGA. The patients have been divided according to *FABP5* expression levels, therefore overall survival is associated with expression levels of FABP5 and patients with a high expression levels have a significantly low overall survival time (P<0.001; Fig. 2A). In addition, patients with UVM and high *FABP5* mRNA levels showed shorter PFS time (P=0.0007; Fig. 2B). Furthermore, the ROC curve was generated to validate the ability of the logistic model to predict prognosis. The AUC index for the integrated model was 0.867 for the OS (P=0.008) for patients with UVM who had died (Fig. S1).

Immune infiltration level. Tumor-infiltrating lymphocytes are an independent predictor of cancer sentinel lymph node status and survival rate (26,27). Therefore, the correlation between *FABP5* expression and immune infiltration levels in UVM was investigated using TIMER. The analysis demonstrated that *FABP5* expression had significant and positive correlation with tumor purity and $CD8^+$ T cells in UVM and significant negative correlation with infiltrating levels of $CD4^+$ T cells and neutrophils in UVM (Fig. 3).

Functional annotation and predicted signaling pathways. The PPI network of FABP5 was constructed. The network of *FABP5* and its co-expressing genes (resistin, ATP citrate lyase, annexin A2, lipase E, Serpin family B member 3, PPARδ, retinoid X receptor α, transthyretin, granulin precursor and S100 calcium binding protein A7) was visualized (Fig. 4A). The PPI network derived from active interaction sources was

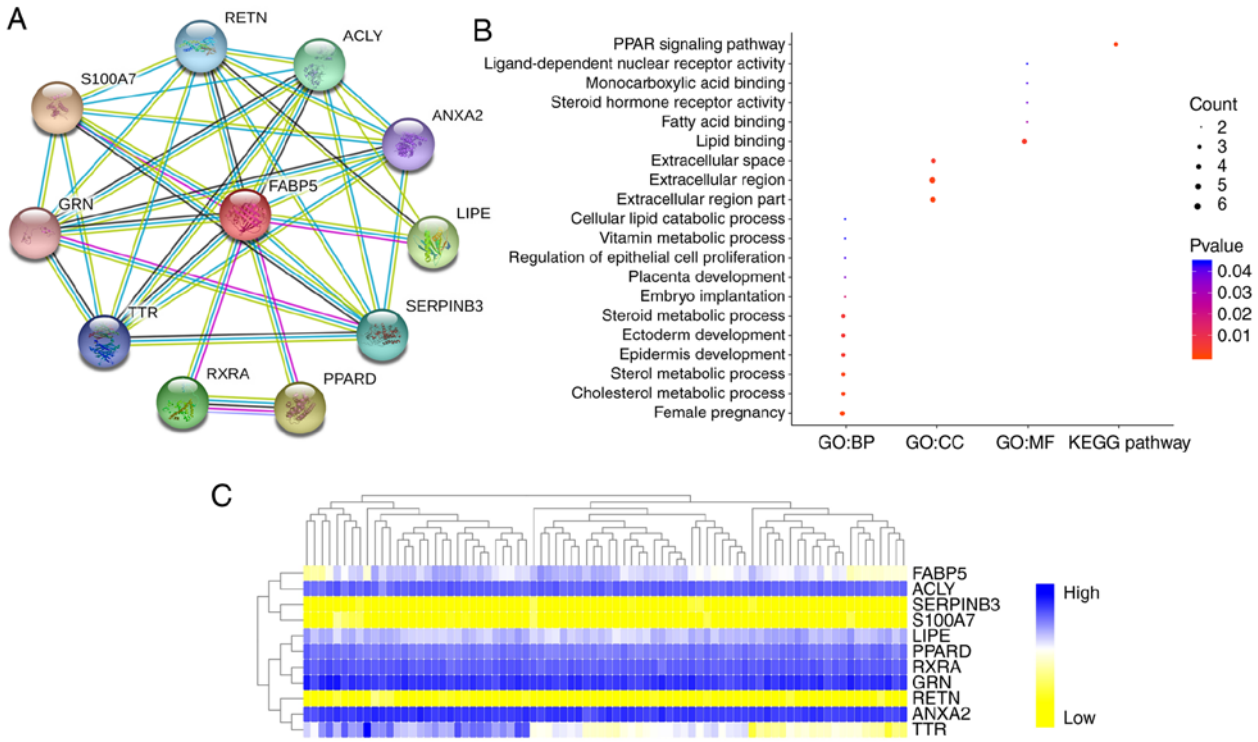

Figure 4. Functional annotations and predicted signaling pathways. (A) The PPI network of *FABP5* was constructed. The network of *FABP5* and its co-expression genes was illustrated visually. (B) Functional and pathway enrichment analyses of a total of 11 genes associated with *FABP5* were performed and visualized using a bubble chart. (C) Hierarchical partitioning of *FABP5* and its co-expressing genes was obtained from DNA microarrays. The expression levels of 11 genes across a number of comparable samples are presented, with high expression marked in blue and low expression marked in yellow. *FABP5*, fatty acid-binding protein 5; PPI, protein-protein interaction; GO, Gene Ontology; BP, biological processes; MF, molecular functions; CC, cellular components; KEGG, Kyoto Encyclopedia of Genes and Genomes.

illustrated in detail with the required interaction score equal to 0.400. As illustrated in Fig. 4B, functional and pathway enrichment analyses of a total of 11 associated genes were performed and visualized using a bubble chart. The changes in the BP of significant genes were significantly enriched for 'female pregnancy', 'cholesterol metabolic process', 'sterol metabolic process', 'epidermis development', 'ectoderm development' and 'steroid metabolic process'. The changes in CC were mostly enriched for the 'extracellular region part', 'extracellular region' and 'extracellular space'. The GO analysis results showed that changes in the MF of significant genes were primarily enriched in 'lipid binding'. The hierarchical partitioning of *FABP5* and its co-expressing genes was obtained from 80 UVM patients of TCGA database (Fig. 4C). It represents the levels of expression of 11 genes across 80 comparable UVM patients from TCGA database with high expression marked in blue and low expression marked in yellow.

Significant genes and pathways obtained by GSEA. A total of 100 significantly associated genes were obtained using GSEA, including those with both positive and negative associations. Importantly, GSEA was used to perform the analysis of hallmark pathways that are associated with *FABP5*. The results suggested the pathways that were significantly associated with *FABP5*, included allograft rejection, complement, interleukin-6/Janus kinase-STAT3 signaling, interferon γ response, inflammatory response and tumor necrosis factor α signaling via NFκB (Fig. 5A-F). In addition, the transcriptional expression profiles of the 100 significant genes were analyzed using a heat map (Fig. 5G).

Discussion

Aberrant genetic and epigenetic regulation of key metabolic pathways is known to contribute towards the development and progression of UVM (28). Elevated expression of the protease A disintegrin and metalloproteinase domain 10 and the membrane transporter ATP binding cassette subfamily B member 5 was shown to be associated with rapid metastatic progression and worse prognosis in UVM, suggesting that these proteins may be useful as prognostic factors (29,30). As a major mediator of fatty acid uptake, transport and metabolism, *FABP5* may participate in the development and aggressive behavior of cancer (7,12,31,32). Accordingly, *FABP5* is known to play an oncogenic role in numerous types of cancer, including prostate carcinogenesis, cervical cancer, renal cell carcinoma and hepatocellular carcinoma (6,8,11,12), however to the best of our knowledge the prognostic implications of FABP5 expression in UVM are currently unknown. In order to address this gap in knowledge; the present study investigated the expression, potential function and prognostic value of *FABP5* in UVM.

FABP5 is an intracellular carrier of long-chain fatty acids and other bioactive lipids and also modulates their metabolism. In addition to transporting fatty acids within the cytoplasm, *FABP5* transfers fatty acids into the nucleus, where they activate transcription factors (33). For example, *FABP5* transfers

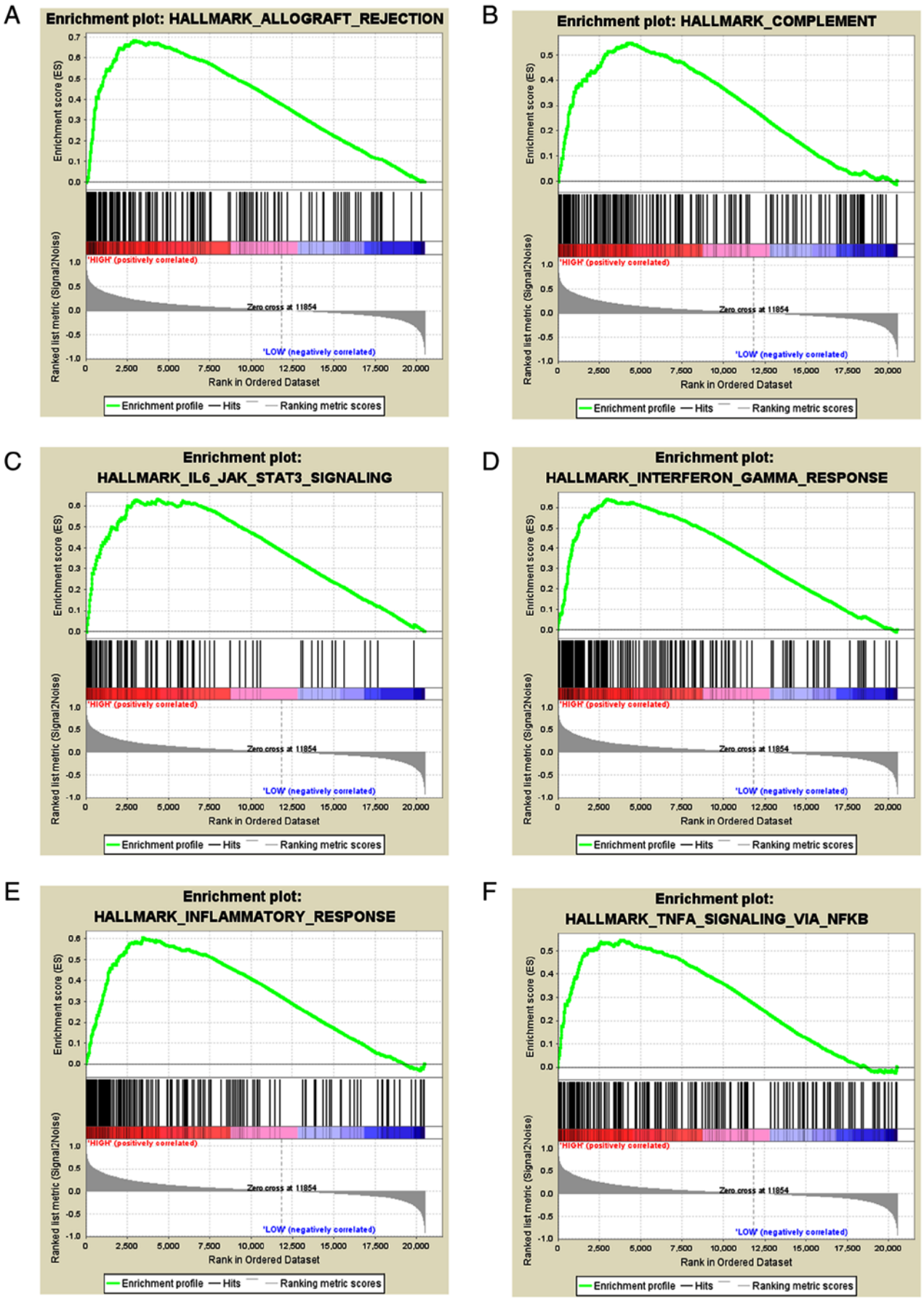

Figure 5. Significantly associated genes and hallmarks pathways in uveal melanoma obtained using GSEA. A total of 100 significant genes were obtained using GSEA with positive and negative associations. (A-F) The most significantly associated pathways included (A) allograft rejection, (B) complement, (C) IL6/JAK-STAT3 signaling, (D) interferon γ response, (E) inflammatory response and (F) TNFA signaling via NFκB. GSEA, Gene Set Enrichment Analysis; IL6, interleukin-6; JAK, Janus kinase; TNFA, tumor necrosis factor α.

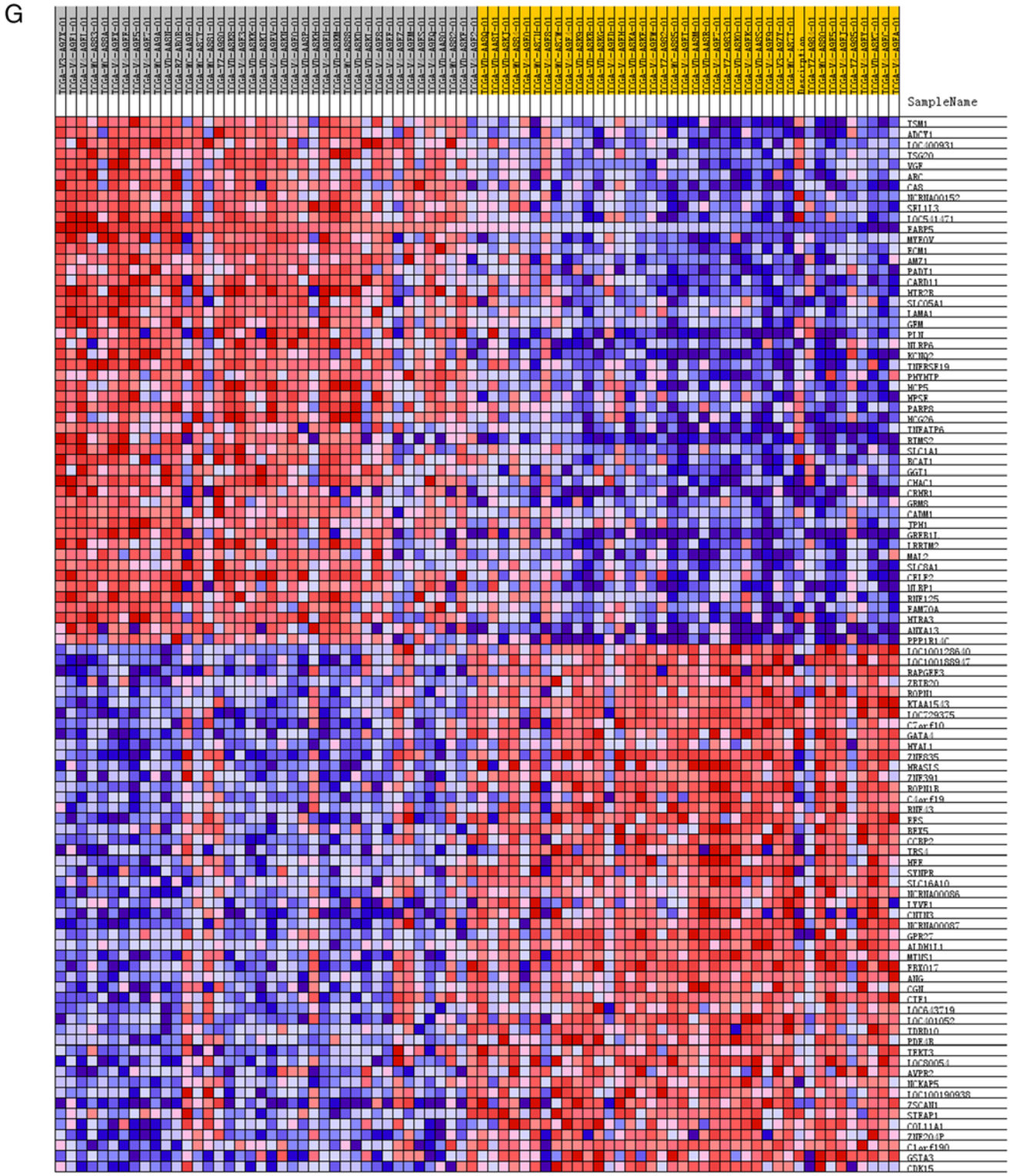

Figure 5. Continued. Significantly associated genes and hallmarks pathways in uveal melanoma obtained using GSEA. A total of 100 significant genes were obtained using GSEA with positive and negative associations. (G) The transcriptional expression profiles of the 100 significant genes are presented as a heat map. The color gradients illustrate high (red) or low (blue) expression levels. GSEA, Gene Set Enrichment Analysis.

retinoic acid to PPARδ, which contributes to cell survival and proliferation, and *FABP5* regulates the induction of prostaglandin E synthase and inflammation via prostaglandin E2 biosynthesis and NFκB activation (34).

Previous studies have shown that *FABP5* expression was associated with the malignant behavior of multiple types of cancer. Among its oncogenic activities, *FABP5* promoted cell migration, proliferation and survival by enhancing the transcriptional activities of nuclear receptor peroxisome proliferator-activated receptor β/δ in human breast cancer cells (MDA-MB-231 cells), human immortalized epidermal cells (HaCaT cells) and human colorectal adenocarcinoma cells (LS-174T cells) (7,35-37). *FABP5* expression was associated with primary and metastatic prostate cancer

and is differentially expressed in primary and metastatic UVM (38,39). Moreover, *FABP5* was suggested as a potential therapeutic target for prostate cancer (40). Furthermore, the expression of *FABP5* was elevated in the regional lymph nodes of patients with vulvar carcinoma, suggesting its potential as a prognostic marker gene for this disease (41). *FABP5* may contribute to retinoic acid resistance and decrease the anticarcinogenic activities of retinoic acid in breast cancer (42).

At the molecular level, elevated *FABP5* expression in fibroblasts was shown to increase PPARδ activity, cell proliferation, migration and invasion in breast cancer (43). In human prostate cancer cells (PC-3 cells) and human breast cancer cells (MDA-MB-231 cells), *FABP5* contributes to inflammatory cytokine production via protein kinase C and the NFκB signaling pathway in response to elevated levels of reactive oxygen species (10). In addition to PPARβ/δ, PI3K/AKT and NFκB activities are involved in the regulation of *FABP5* activity and expression. *FABP5* may increase clear cell renal cell carcinoma cell proliferation, partly via the PI3K/AKT signaling pathway (11). In colorectal cancer, *FABP5* promoted cell growth and metastasis via the PPARβ/δ signaling pathway (15). In addition, *FABP5* promoted the expression of secreted proteins associated with tumor malignancy, by activating the NFκB signaling pathway (10).

To the best of our knowledge, the present study is the first to investigate the potential of *FABP5* as a prognostic factor of UVM. Although *FABP5* has been implicated in the development of numerous types of cancer and other human diseases, including prostate cancer, intrahepatic cholangiocarcinoma, colorectal cancer and cervical cancer (7,8,12,14,15), little is known about its involvement in UVM. The present study demonstrated that the mRNA expression levels of *FABP5* was elevated in UVM tissues, which was significantly associated with worse clinicopathological parameters, such as shorter OS and PFS times. Of note, another study demonstrated that patients with spindle cell UVM tumors had longer disease-specific survival compared with those with epithelioid and mixed tumors consisting of epithelioid and spindle cells (44). This association was linked to the expression levels of *FABP5* mRNA, with the highest being observed in epithelioid UVM and the lowest in spindle cell UVM. Furthermore, younger patients (≤20 years) with UVM at the time of diagnosis were found to have a lower rate of metastasis compared with adults (21-60 years) and older adults (>60 years), which indicated the risk of metastasis gradually increased with increasing age (45-47). In the present study, the transcriptional expression of *FABP5* in UVM was significantly associated with the age of the patient suggesting it has prognostic value patients with UVM. Furthermore, two additional major findings from the present study reveal that *FABP5* expression was positively correlated with UVM tumor purity and $CD8^+$ T cells whereas it was negatively correlated with immune cell infiltration; specifically, with the number of $CD4^+$ T cells and neutrophils. These data suggests that *FABP5* may play a crucial role in immune cell recruitment to and/or retention within the tumor microenvironment in UVM.

There are several limitations to the present study. Firstly, only *FABP5* mRNA expression levels were examined as a potential prognostic biomarker to predict OS and PFS times. Secondly, further validation studies or prospective cohorts should be analyzed to verify the present findings. Finally, despite conducting bioinformatics analysis of functional annotations and enrichment of *FABP5*-associated pathways, these findings were not verified by exploring the underlying molecular mechanisms of *FABP5* signaling. Thus, further studies will be required to understand the association between *FABP5* and tumor growth in UVM, as well as in other cancer types.

To the best of our knowledge, the present study is the first to reveal that elevated *FABP5* expression is significantly associated with cancer progression and poor survival in patients with UVM. Thus, *FABP5* is a potential marker of UVM, which is easily detected, thereby assisting in the selection of monitoring and treatment strategies. The present study also provides novel directions for further studies, in order to elucidate the molecular pathogenesis of UVM. Such studies, together with randomized clinical trials, will be required to understand the precise underlying mechanisms of action of *FABP5* and its clinical application in patients with UVM.

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Availability of data and material

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XFZ designed the research and contributed towards the analyses, interpretation and presentation of data. YX and WHX drafted the manuscript, analyzed the data and interpreted the results. XLY helped to perform the statistical analysis and the literature review. HLZ co-worked on associated data collection, data interpretation and revising the draft. All authors read and approved the final manuscript.

Ethical approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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