Stage-Wise Gene Expression Profiling Reveals Potential Genes and the Pathways in Kidney Cancer

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Abstract

Micro-abstract: Using the publicly available datasets, we have investigated the list of critical pathways and the genes which appear to be clinically highly significant in case of renal cell carcinoma. ARHGAP6, TGM4, CD248, SLC13A3, EPO, PARD6A, CLCA2, UBE2S, ERAL1, FGFR1, MRVI1, DYNC1I2, CDCA7 are among the top ranked genes which appeared highly significant in terms of patient survival.

Clinical practice points: Using the publicly available datasets, we have investigated the gene expression profiling for renal cell carcinoma. In the previous work, it has been focused on selected genes and pathways. Here, we have investigated the list of critical pathways and the genes which appear to be clinically highly significant in case of renal cell carcinoma. ARHGAP6, TGM4, CD248, SLC13A3, EPO, PARD6A, CLCA2, UBE2S, ERAL1, FGFR1, MRVI1, DYNC1I2, CDCA7 are among the top ranked genes which appeared highly significant in terms of patient survival. These genes leads to potential alteration in PI3K-Akt, Foxo, endocytosis, MAPK, tight junction, cytokine-cytokine receptor interaction pathways. Our work will help in diagnosing the renal cell carcinoma patients because here, we have presented the differentially expressed genes, their inferred pathways, and the clinical impact of the selective genes. Since, our finding is from overall perspective including clinical relevance so this study will help in future for diagnostic also.

Background: Cancer is among the highly complex disease and renal cell carcinoma is the sixth-leading cause of cancer death. In order to understand complex diseases such as cancer, diabetes and kidney diseases, high-throughput data are generated at large scale and it has helped in the research and diagnostic advancement. However, to unravel the meaningful information from such large datasets for comprehensive and minute understanding of cell phenotypes and disease pathophysiology remains a trivial challenge and also the molecular events leading to disease onset and progression are not well understood.

Methods: With this goal, we have collected gene expression datasets from publicly available dataset which are for two different stages (I and II) for renal cell carcinoma.

Results and conclusion: In this work, we have applied computational approach to unravel the differentially expressed genes, their networks for the enriched pathways. Based on our results, we conclude that among the most dominantly altered pathways for renal cell carcinoma, are PI3K-Akt, Foxo, endocytosis, MAPK, Tight junction, cytokine-cytokine receptor interaction pathways and the major source of alteration for these pathways are MAP3K13, CHAF1A, FDX1, ARHGAP26, ITGBL1, C10orf118, MTO1, LAMP2, STAMBP, DLC1, NSMAF, YY1, TPGS2, SCARB2, PRSS23, SYNJ1, CNPPD1, PPP2R5E. In terms of clinical significance, there are large number of differentially expressed genes which appears to be playing critical roles in survival.

Introduction:

Renal cell carcinoma is one of the most common cancers, and it is one of the leading causes of cancer death. High-throughput data is created at a large scale in order to understand complex diseases like cancer, and it has aided in research and diagnostic advancement[1–4]. However, extracting useful knowledge from such vast datasets for a complete and detailed understanding of cell phenotypes and disease pathophysiology remains a difficult task, and the molecular events that contribute to disease initiation and progression are still poorly understood[5–7]. The advancement of the post-genomics period has resulted in a huge amount of "big data" in biological sciences, which has led to a multitude of interdisciplinary applications in recent decades[3,8]. There are a number of biological databases that house various types of datasets. TCGA, oncomine, nephroseq, and GEO (gene expression omnibus) are the most widely used databases in biological sciences[9]. These databases mainly GEO store vast amount of datasets related with cancer, diabetes, and other biological problems[6,10–14].

The identification of pathogenetically distinct tumour types poses a significant challenge in the treatment of complex diseases (especially cancer)[15–17]. The improvement in tumor classification always helps in the improvement during therapeutic approaches[18,19]. In target specific therapy, effectiveness can be maximised while toxicity is reduced by using enhanced classification. To access biological datasets from these databases previously, a variety of tools/approaches were used. For molecular classification of cancer Golub TR *et al.*, [20] have divided cancer classification into two challenges as class discovery and class prediction.

We chose a renal cell carcinoma (RCC) dataset with samples from two stages (stages I and II) for the purpose of understanding how gene expression patterns vary and how altered gene expression patterns lead to possible changes in the respective inferred functions as tumour stage I to II changes and from affymetrix platforms (U133A to U133B).

Here, we have selected a dataset from gene expression omnibus (GEO) where the samples are from human with two tumor stages (I and II). We have organized the samples in the order such as stage I normal versus tumor and stage II normal versus tumor for the affymetrix platforms U133A and U133B and analyzed the tumor samples with respect to their respective controls (normal sample of the same stage) for the gene expression alterations and evolved functions with the increase in tumor percentage. Based on our work, we conclude that irrespective of the tumor stage PI3K-Akt, Foxo, endocytosis, MAPK, Tight junction, cytokine-cytokine receptor interaction pathways and the major source of alteration for these pathways are MAP3K13, CHAF1A, FDX1, ARHGAP26, ITGBL1, C10orf118, MTO1, LAMP2, STAMBP, DLC1, NSMAF, YY1, TPGS2, SCARB2, PRSS23, SYNJ1, CNPPD1, PPP2R5E. In addition, we have also studied the clinical significance and observe that there are large number of differentially expressed genes which appears to be playing critical roles in for survival such as ARHGAP6, TGM4, CD248, SLC13A3, EPO, PARD6A, CLCA2, UBE2S, ERAL1, FGFR1, MRVI1, DYNC1I2, CDCA7.

Methods:

In the first step, we selected the data of interest (raw expression dataset GSE6344) and processed it until normalisation and log2 values of all mapped genes were achieved, as shown in Figure 1a of the workflow. There are 40 samples in this dataset (5 normal and 5 tumour for two stages I and II from U133A and U133B platforms). We compared tumour samples with standard samples of the respective stages and platforms for differential gene expression analysis, yielding four DEGs lists.

In short the basic steps involved for the entire study are raw file processing, intensity calculation and normalization. For normalization[27-29], GCRMA[30-34], RMA, and EB are the most commonly used approaches. Here, we have used EB for raw intensity normalization. After normalization, we proceed for our goal which is to understand the gene expression patterns[12,35] and its inferred functions[35,36].

For differential gene expression prediction and statistical analysis, MATLAB functions (e.g., mattest) has been used. For pathway analysis, we used KEGG[37] database and have our own code designed to pathway and network analysis[38-41].

For generating DEGs network, FunCoup2.0[42] has been used for all the networks throughout the work and cytoscape[43] has been used for network visualization. For most of our coding and calculations MATLAB has been used[38-41]. Protein complexes, protein-protein physical interactions, metabolic, and signalling pathways are among the four types of functional coupling or associations predicted by FunCoup [44].

Results:

In the first step, we have selected the data of our interest (raw expression dataset) GSE6344[21,22], organized the samples in the order such as stage I normal versus tumor and stage II normal versus tumor for the affymetrix platforms U133A and U133B and processed it until normalization and log2 values for all the mapped genes as mentioned in the workflow Figure 1a. This dataset contains 40 samples (5 normal and 5 tumor for two stages I and II from U133A and U133B platforms). For differential gene expression analysis, we have compared the tumor samples with normal samples of the respective stages and the respective platforms that it gives us four DEGs lists.

Gene expression profiling and the associated functions for varying tumor percentages: In this study, the initial focus of our goal was to understand the gene expression pattern between the different stages for normal versus tumor samples. For this purpose, the total number of the DEGs, up, and down regulated genes have been calculated (Figure 1b) and observe that the number of down regulated genes are comparatively high in all the four DEGs list (Figure 1c). For U133A dataset, we observe very high number of DEGs for same stage and shares 1147 genes between stage I and II with respect to U133B which is 606 genes and stage I and II specific genes are also high in both the platforms U133A and U133B. Similar to DEGs sharing the enriched pathways are also distributed in the similar trend as shown in Figure 1d (p-values < 0.05) and Figure 1e (p-values < 0.001). Most of the shared genes between different stages and platforms have been shown with their fold changes and these genes are known to be associated with the critical pathways which are very important for multiple type of cancers (Figure 1f). In addition, we have

also mapped the known association between all these genes (from Figure 1f) in the form of network as s in Figure 1g.

Top ranked enriched pathways for the respective DEGs list: After analyzing the number of DEGs and enriched pathways, we have analyzed the enriched pathways and the genes which are altered in different RCC tumor stages (Table 1). We observe that MAPK, cytokine, Akt, Wnt, hippo, Hif1, metabolic signaling pathways are the top ranked pathways which are frequently altered and their potential source of alterations are MAP3K13, CHAF1A, FDX1, ARHGAP26, ITGBL1, C10orf118, MTO1, LAMP2, STAMBP, DLC1, NSMAF, YY1, TPGS2, SCARB2, PRSS23, SYNJ1, CNPPD1, PPP2R5E. These genes and the pathways are known to play the potential roles directly or indirectly in case of cancer.

Network-level understanding of the DEGs: Based on the venn diagram of the enriched pathways, we have prepared the list of the pathways in five groups (commonly enriched) and matched the genes with these pathways lists from all the four DEGs list (normal versus tumor in stage I and II for the U133A and U133B datasets). In Figure 2, the networks have been shown for stage I of U133A, Stage I and II of U133B datasets. The networks shown are for those DEGs which are matching to different pathways lists obtained during venn diagram drawing. The major pathways have been highlighted on the top of the figure and in the left side the tumor stage have been mentioned. Since most of the networks for stage II of U133A dataset were densely connected so for such networks we have presented top 30 genes in terms of connectivity within the network (Figure 3). Here, we have also shown the connectivity of the genes for those networks where the connections are not clearly visible. For more details of the list of the pathways used for the network have been supplied in the supplementary data (S1).

Clinical significance of the differentially expressed genes: Additionally, we have selected the top ranked genes (based on the fold change 15 up and 15 down) and analyzed the patients survival (kaplan-meier plot) for the patient samples from TCGA database. We observe that most of the top-raked genes (from selected 30 DEGs) mainly up-regulated genes show very high significance on the patients survival (Figure 4). In this figure, we have also shown the mutations in these top-ranked DEGs for clear renal cell carcinoma in the TCGA databse. There are few genes which are mutated at very high rate as shown in Figure 4a and 4b. Kaplan-Meier plots show the clinical significance and that is a large number of differentially expressed genes appear to be potentially significant in terms of survival and some of the selected genes are ARHGAP6, TGM4, CD248, SLC13A3, EPO, PARD6A, CLCA2, UBE2S, ERAL1, FGFR1, MRVI1, DYNC1I2, CDCA7 (additional data shown in supplementary figures S1—S6).

Discussion:

Renal cell carcinoma is one of the most common cancers, and it is one of the leading causes of cancer death[12,13,23]. In terms of therapy and diagnosis, therapeutic and clinical outcomes differ between the individuals with even close similarity in clinical and pathological characteristics (tumor type, grades, and stages) and despite tremendous efforts to identify molecular biomarkers (prognostic and predictive) and with improved precision compared to clinical and pathological predictors only few molecular tests have

been introduced into oncological practice[24]. So it is important to understand and unravel different levels (such as gene expression pattern, epigenetics, protein expression) of diversities in cancer[25,26]. We gathered the previously published dataset for this purpose and conducted a detailed and precise study ranging from gene expression profiling to functional changes, including networks mapped from the human protein network database.

Our work leads to the conclusion that irrespective of the tumor stage PI3K-Akt, Foxo, endocytosis, MAPK, Tight junction, cytokine-cytokine receptor interaction pathways and the major source of alteration for these pathways are MAP3K13, CHAF1A, FDX1, ARHGAP26, ITGBL1, C10orf118, MTO1, LAMP2, STAMBP, DLC1, NSMAF, YY1, TPGS2, SCARB2, PRSS23, SYNJ1, CNPPD1, PPP2R5E. Networks of DEGs for the enriched pathways show that there are large number of genes from few specific pathways are altered such as Ras signaling pathways(Fig. 2c, h, and m), immune sysytems, Wnt, hippo, (Fig. 2d, i, and n) Akt pathways (Fig. 2a, f, and k). Here, we observe that critical pathways altered in RCC are wnt, hippo, regulation of actin cytoskeleton, ECM, infection and inflammation, metabolic, and more cancer related pathways. From the mapped network, we observe that the highly connected genes infer the potential pathways or in other works the top ranked genes based on connectivity refer to those pathways which are directly or indirectly associated either with RCC or other types of cancer.

In terms of clinical significance, we looked at the rate of mutations for the top ranked genes (based on fold change) and patients' survival for changes in gene expression, with Kaplan-Meier plots indicating clinical significance. We conclude that a large number of differentially expressed genes tend to be potentially important in terms of survival, with ARHGAP6, TGM4, CD248, SLC13A3, EPO, PARD6A, CLCA2, UBE2S, ERAL1, FGFR1, MRVI1, DYNC1I2, CDCA7 among the genes chosen.

Conclusions:

Based on our findings, we conclude that PI3K-Akt, Foxo, endocytosis, MAPK, Tight junction, and cytokine-cytokine receptor interaction pathways are among the most commonly altered pathways in renal cell carcinoma, and that MAP3K13, CHAF1A, FDX1, ARHGAP26, ITGBL1, C10orf118, MTO1, LAMP2, STAMBP, DLC1, NSMAF, YY1, TPGS2, SCARB2, PRSS23, SYNJ1, CNPPD1, and PPP2R5E are the major sources of alteration for these pathways. Wnt, hippo, actin cytoskeleton control, ECM, infection and inflammation, metabolic, and other cancer-related pathways are among the most important pathways altered in RCC. ARHGAP6, TGM4, CD248, SLC13A3, EPO, PARD6A, CLCA2, UBE2S, ERAL1, FGFR1, MRVI1, DYNC1I2, CDCA7 are some of the genes that were chosen after survival study.

Declarations:

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Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE: Not Applicable.

HUMAN AND ANIMAL RIGHTS: Not Applicable.

CONSENT FOR PUBLICATION: Not applicable.

AVAILABILITY OF DATA AND MATERIALS: We have utilized the publicly available datasets (main data source) which are freely available and have mentioned it in method section with proper references. The analyzed details have been supported by the supplementary data.

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HIK, IMA, LHB, PKPK, MAK, and MM designed the experiment, performed calculations, analyzed the results and written the manuscript. HIK, IMA, LHB, PKPK, MAK, and MM contributed in designing the experiment, analysis, and manuscript writing. HIK, MAK, and MM contributed in experiment designing, analysis, and manuscript writing. The work has been supported by the Deanship of Scientific Research (DSR) at King Abdulaziz University, Jeddah, Saudi Arabia funded this project, under grant no. (422-800).

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Tables:

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

Figures

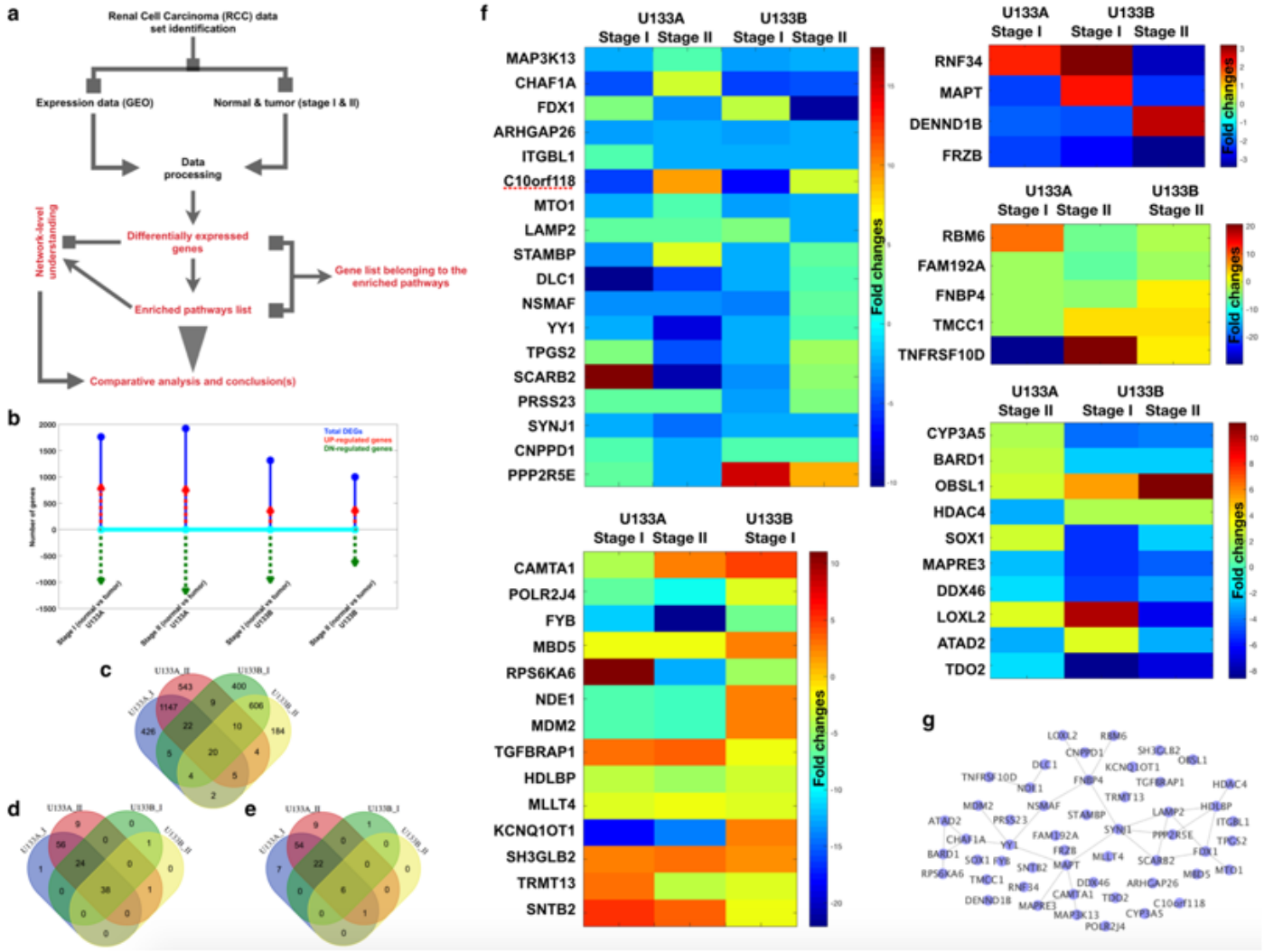

Figure 1

Gene expression profiling. (a) Workflow: from raw dataset to analysis. (b) Number of DEGs, up- and down-regulated genes. (c) Venn diagram to display the DEGs. (d) Venn diagram for enriched pathways for the DEGs (p-value <= 0.05). (e) Venn diagram for enriched pathways for the DEGs (p-value <= 0.001). (f) Common genes between different stages and the array chips (U133A and U133B) with their fold changes. (g) Mapped network for all the genes in (f).

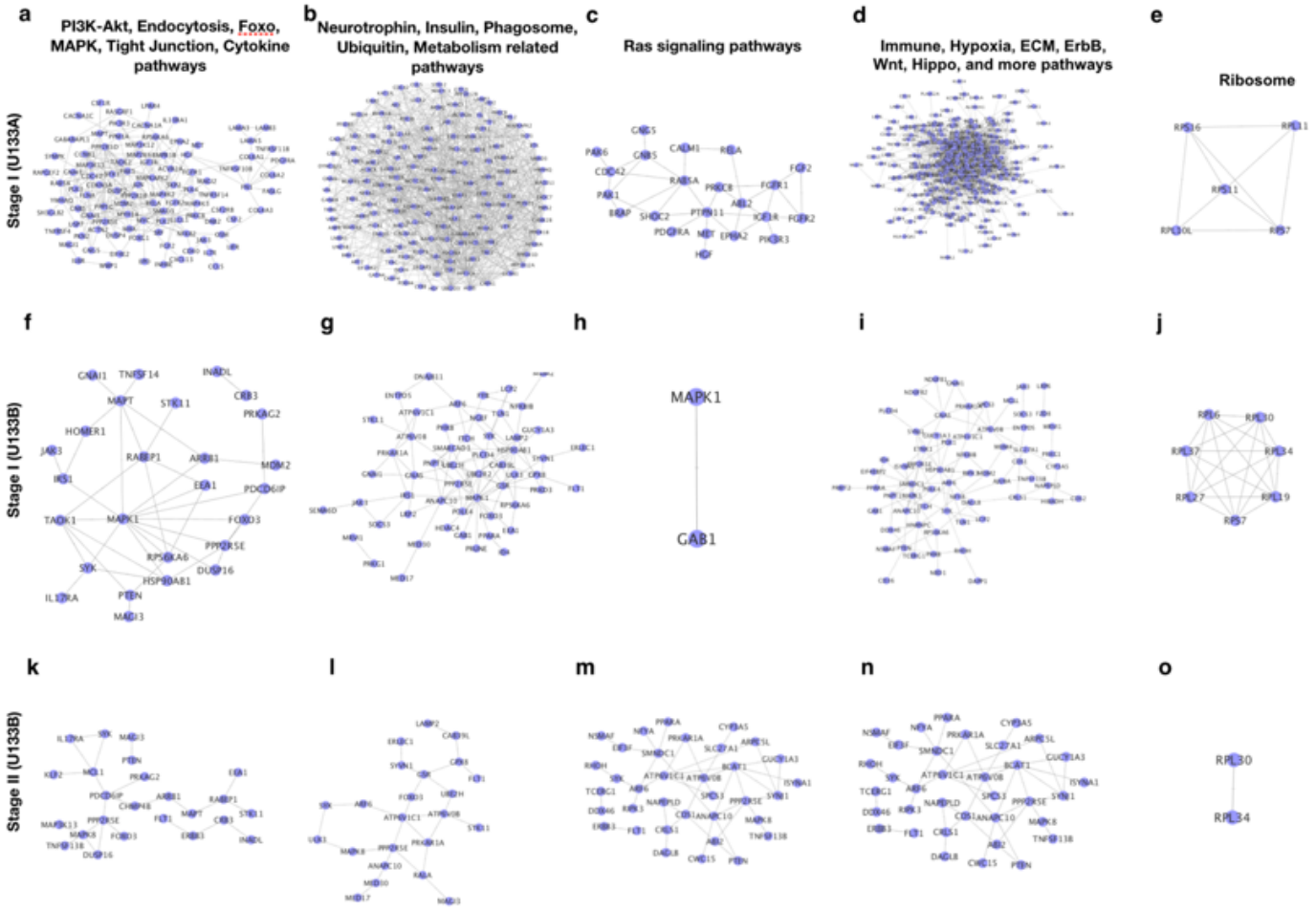

Figure 2

Networks for the genes matched with those pathways which are enriched (p-values <= 0.001) and common shown in venn diagram for all the four DEGs list (Stage I and II for U133A and U1333B). In this figure, we have selected those pathways which are commonly enriched pathways and mapped the genes belonging to these pathways from the DEGs list and finally mapped out the networks. (a) – (e) It represents the networks for Stage I of U133A platform data for the list of pathways. (f) – (j) It represents the networks for Stage I of U133B platform data for the list of pathways. (k) – (o) It represents the networks for Stage II of U133B platform data for the list of pathways.

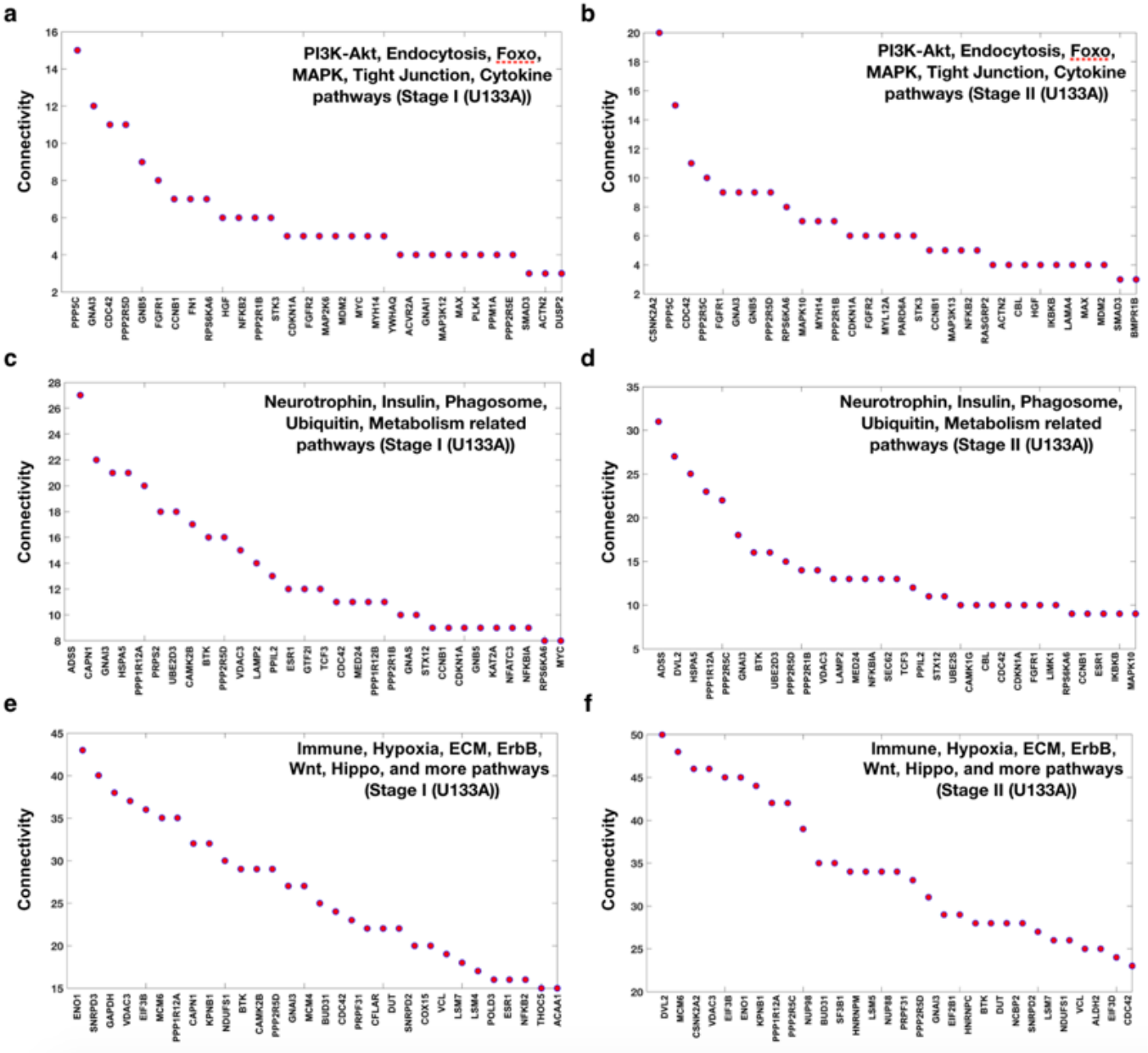

Figure 3

Connectivity in the selected networks (where the gene connectivity is not visible), for the top 30 genes matched with those pathways which are enriched for the DEGs list. (a) – (f) Connectivity of the genes in the network for Stage I and II of U133A.

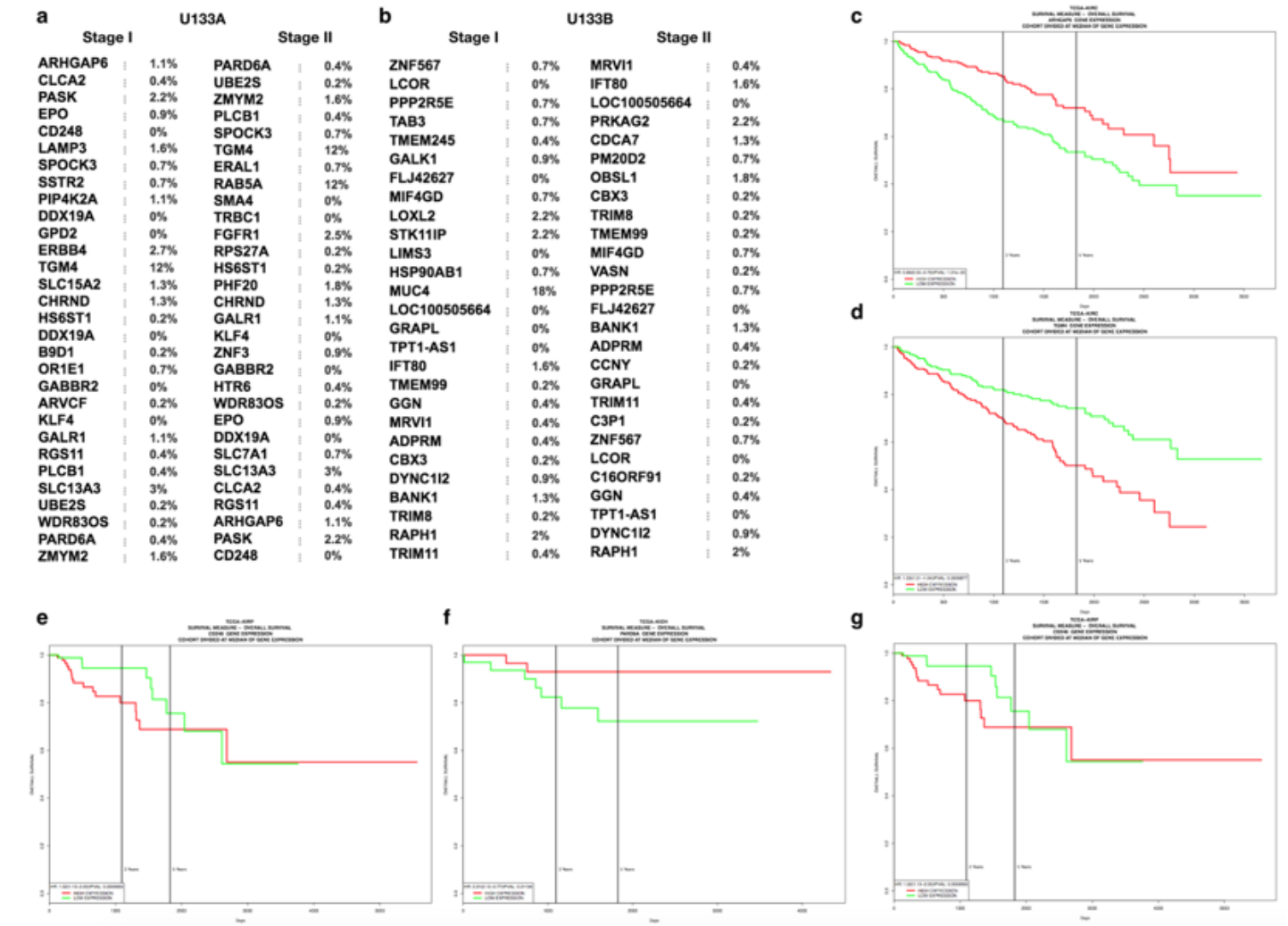

Figure 4

Clinical significance of the top ranked genes. (a) and (b) Top 30 (15 up and down) DEGs (based on fold change) with the rate of mutation in kidney renal clear cell carcinoma (TCGA) with their mutations. (c)—(g) Survival plots for the selected top ranked genes.

Supplementary Files

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- Table1.pdf
- Figuress1s6.pdf