Target-based Drug Repositioning in Papillary Renal Cell Carcinoma with *TFE3* Fusions



Sung Joo Han, Sejoon Lee, Jae Won Yun*, and Soyeon Ahn*

Medical Research Collaborating Center, Seoul National University Bundang Hospital, Seongnam 13620, Korea

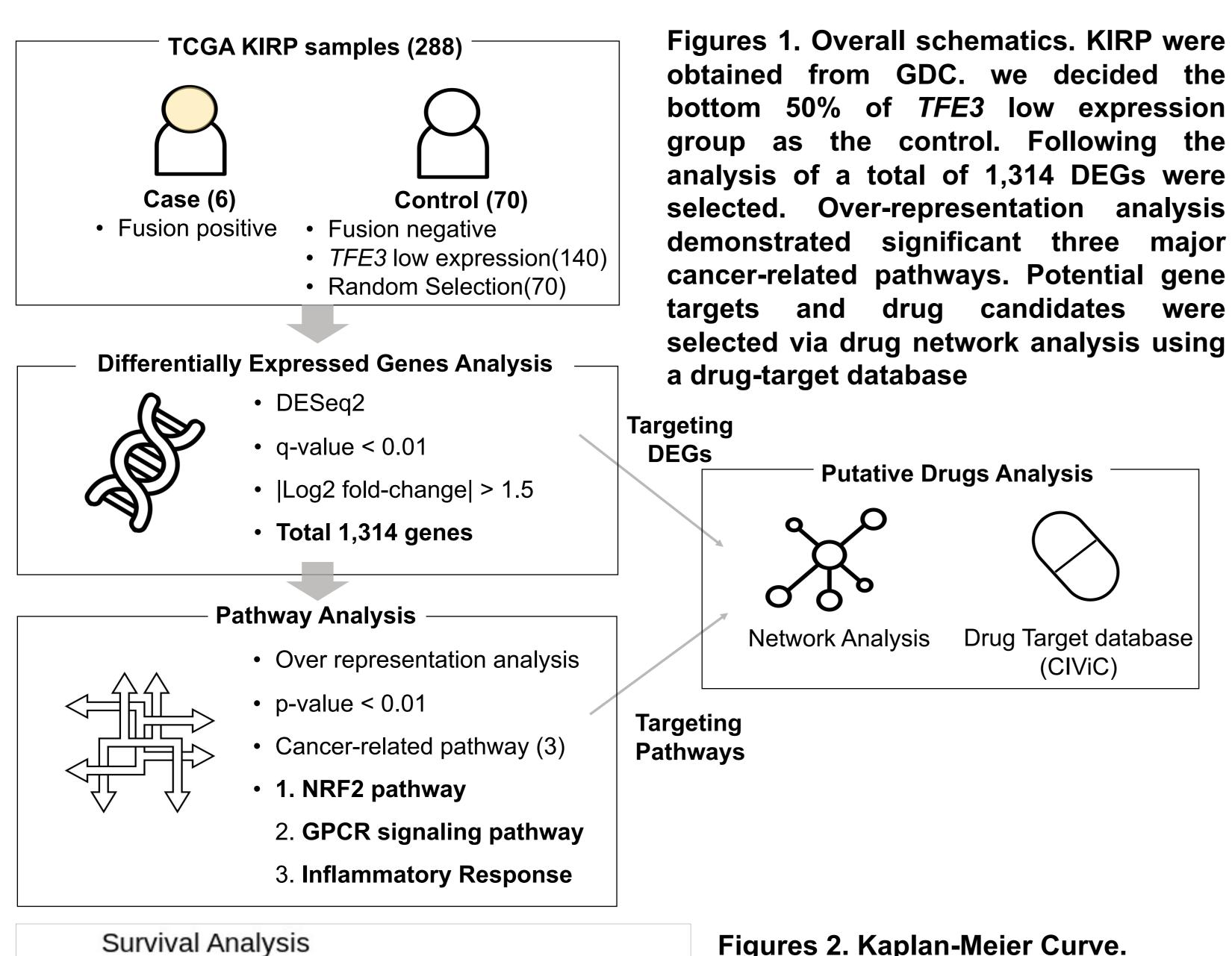
Abstract

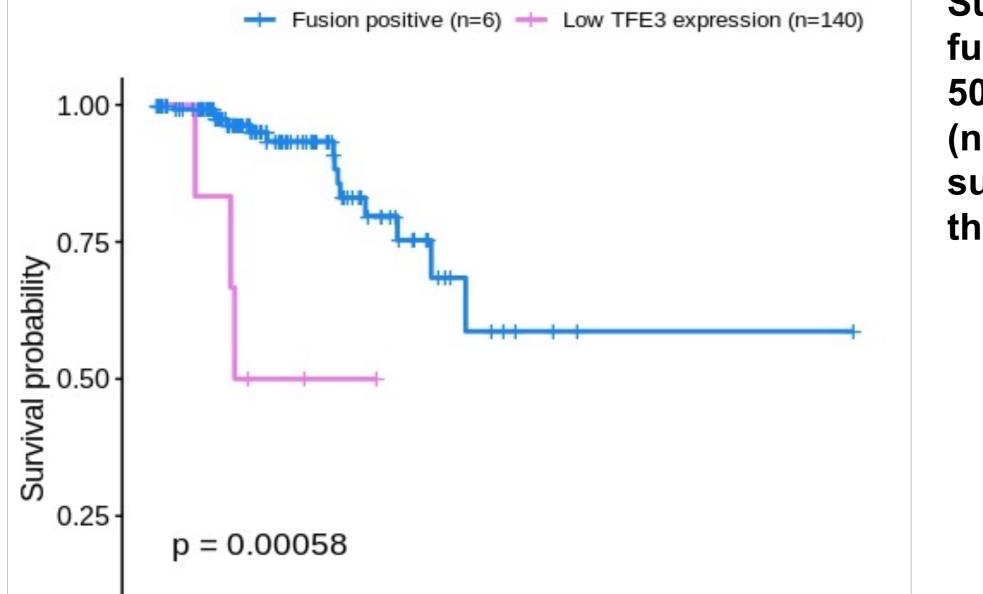
- Papillary renal cell carcinoma (PRCC) had the highest ratio of TFE3 fusion and PRCC with TFE3 fusions showed aggressive phenotype.
 Nevertheless, effective targeted therapies for such patients are yet to be identified till now.
- Therefore, the aim of this study is to elucidate of novel therapeutic targets by applying systematic bioinformatical analysis for PRCC with *TFE3* fusion.
- A total of 288 samples with PRCC was obtained from TCGA including 6 fusion cases. A total of 1,314 differentially expressed genes (DEGs) and three major signaling pathways were extracted by performing transcriptome analysis and statistical analysis.
- Potentially applicable drug candidates targeting the DEGs or the major signaling pathways were selected by using drug-target network analysis. Finally, amrubicin, cetuximab, panitumumab, paclitaxel, and epirubicin were considered promising drug candidates for PRCC with *TFE3* fusion.

Introduction

- PRCC is the second most common subtype of renal cell carcinoma. PRCC have associated with gene fusions involving *TFE3* which had the highest ratio in TCGA patients [1]. Moreover, the clinical behaviour with *TFE3* fusion showed relatively aggressive phenotype [2].
- We systematically analyzed the molecular features of *TFE3* in PRCC and finding DEGs, performing network analysis and targeting drugs.
- In TCGA kidney papillary renal cell carcinoma (KIRP) data, *TFE3* fusion positive samples showed significant correlation with *TFE3* high expression. Moreover, half of them belongs to the top 10% in *TFE3* expression.

Results





3000

Time

5000

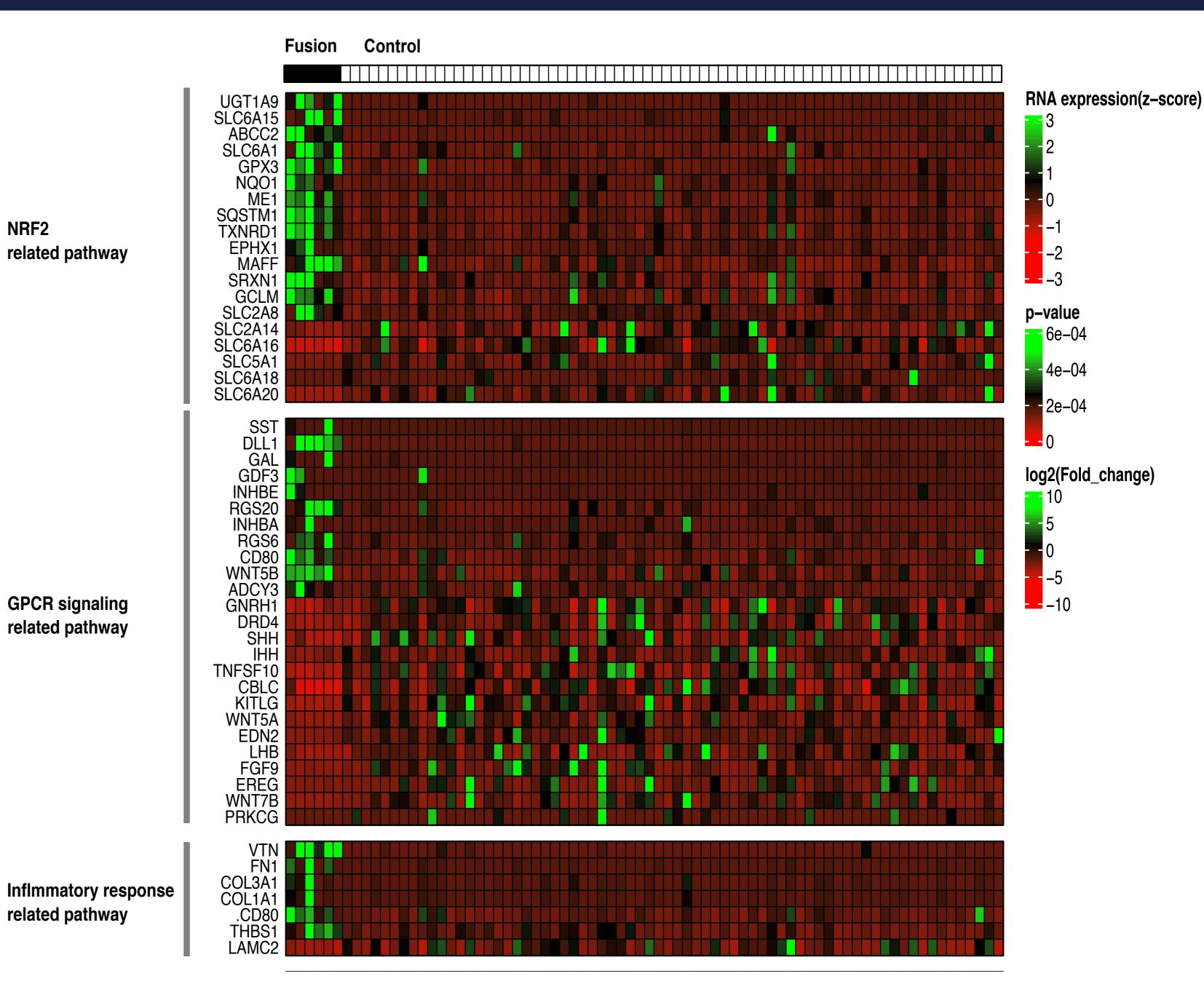
4000

6000

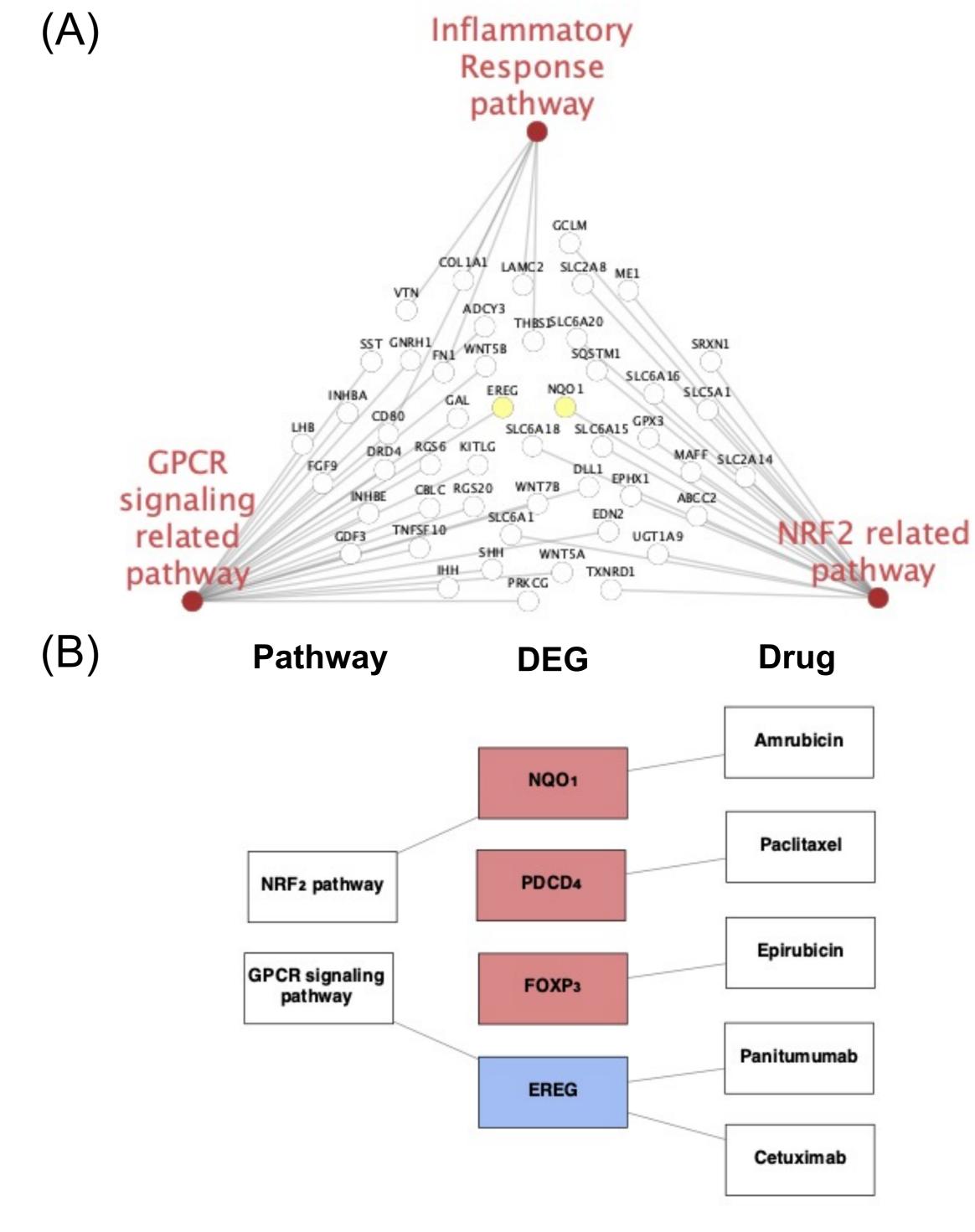
2000

1000

Figures 2. Kaplan-Meier Curve. Survival Analysis between the fusion case (n=6) and the bottom 50% of low *TFE3* expression (n=140). The plot represented the survival rate difference between the case and control (P <0.001).



Figures 3. Gene expression heatmap of cancer-related pathways using the DEGs. Expression value of DEGs associated with NRF2 related pathway, GPCR signaling related pathway, and Inflammatory response related pathway demonstrated significant differences between fusion positive and control.



Figures 4. Visualization of network between putative target genes, the cancer-related pathways, and target drugs. (A) Three major cancer-related pathways and associated genes. (B) Drug-target network. Left: the major cancer signaling pathways; center: genes; right: drugs. Red: over-expressed genes in fusion positive case; blue: under-expressed genes.

Conclusion

We identified the DEGs in PRCC with *TFE3* fusion and the shared pathways that has potential to predict therapeutic targets.

References

[1] Comprehensive molecular characterization of papillary renal-cell carcinoma. (2016). New England Journal of Medicine, 374(2), 135–145. https://doi.org/10.1056/

[2] Kauffman, E. C., Ricketts, C. J., Rais-Bahrami, S., Yang, Y., Merino, M. J., Bottaro, D. P., Srinivasan, R., & Linehan, W. M. (2014). Molecular genetics and cellular features of TFE3 and TFEB fusion kidney cancers. Nature Reviews Urology, 11(8), 465–475. https://doi.org/10.1038/nrurol.2014.162

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), which is funded by the Ministry of Education (NRF-2015R1D1A1A02061597) and by Seoul National University Bundang Hospital (grant number 18-2018-005) to SA. This study was supported by a VHS Medical Center Research Grant, Republic of Korea (VHSMC21038) to JW.