Author's response to reviews

Title: Identifying Significant Genetic Regulatory Networks in the Prostate Cancer from Microarray Data Based on Transcription Factor Analysis and Conditional Independency

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Author's response to reviews: see over
Summary for Revision II

Identifying Significant Genetic Regulatory Networks in the Prostate Cancer from Microarray Data Based on Transcription Factor Analysis and Conditional Independency

We appreciate the comments from the associate editor and all reviewers in this paper. We have made necessary experiments and modifications to cope with all the comments.

The basic notations for different fonts are:
- **Bold face** fonts are from reviewers’ original comments.
- *Italic face* fonts are the modified/adDED texts in the paper.
- Plain fonts are our answers to reviewers’ comments.

Answers to Reviewer #1

Q1: The authors should provide more detailed information about the multiple test corrections they conducted in this study. For example, during the procedure to generate initial gene network (pg.11), what is the threshold for Bonferroni correction in order to identify dependent genes and how many genes passed the test and were used for further analysis? Usually this step will filter out many candidates and thus change the reconstructed regulation network significantly. However, it is weird to find out the results of network analysis shown in figure 9, 10, 12 and 13 in the new manuscript are totally unchanged (see figure 7, 8, 10 and 11 in the old version for comparison). Therefore, the authors should provide more data (like the networks generated with/without Bonferroni correction) to prove that the new networks will generate exactly the same results as shown in these figures.

A1: Thanks for your comments for the detail information and our mistake in interpretation some figures. In page 10, it is only one hypothesis testing for a transcript regulatory gene and the other gene in the microarray data. There are just two variables to do the hypothesis independent testing with chi-square method and the significant p-value is still 0.05. After we get the pair of interactions from transcription regulatory genes and their co-expressed genes, we start to check the indirect edges should be needed and it may included several variables to be tested. For the traditional constraint-based method, it is no way to avoid an exponential number on conditional
independence testing for every pair of nodes to make sure that the indirect edges should be kept or removed according to the different genes combinations [14]. For a given structure, we choose a pair of nodes with special structure (the concept of d-separation see in figure 4) and begin to do the local search for a certain set that is guaranteed to be minimum d-separating sets between pair of genes. The method of searching local casual relationships to be simple and fast and it will be will gain computational efficiency comparing with considering all the relationships of all the nodes in the networks [14].

We use the "finding the minimum d-separating sets procedure" in Figure 5 to extract the minimum d-separate genes between start and end genes and we determine whether an edge between two nodes should be removed. There are repeated tests of conditional independencies given minimum d-separating sets so we apply Bonferroni correction for multiple testing to renew the significant threshold for each of the n individual tests to maintain an experiment-wise error rate. Take an example, if the minimum d-separating genes \{C,D\} between gene A and gene B, the minimal basis set contains 2 multiple test simultaneously for genes A and B which are d-separated by gene C and gene D and any one of tests rejects the null hypothesis that the pairs are independent of A and B gene. In this case, two independent hypotheses testing on the same data at 0.05 significance level may be instead of 0.025 (0.05/2). For different d-separated genes, we can get different significant p-value and so on.

After the Bonferroni correction for conditional independence testing, we extract 8,298 interactions in cancer network in table 6 and we modify the logarithmic plot of degree distribution and clustering coefficient in figure 9, 10 and table 8. We provide the information of 95 links (=8,393-8,298) after using Bonferroni correction in Additional file 13 in cancer network. We also provide the p-value of each pair of genes with independent testing in Additional file 12 to show why the figures are still the same after Bonferroni correction.

On P.10 line 24 and P.11 line 1

There are just two variables to do one hypothesis independent testing with chi-square method and the significant p-value is still 0.05.

On P.16 line 3-15

For the traditional constraint-based method, it is no way to avoid an exponential number on CI tests for every pair of nodes to make sure that the edges should be kept or removed [14]. After we find the minimum d-separating sets, we determine whether an indirect edge between two nodes should be needed and there are repeated tests of conditional independencies given minimum d-separating sets. We apply Bonferroni
correction for multiple testing to renew the significant threshold for each of the n 
individual tests to maintain an experiment-wise error rate. Take an example, if the 
minimum d-separating genes {C,D} between gene A and gene B, the minimal basis set 
contains 2 multiple test simultaneously for genes A and B which are d-separated by 
gene C and gene D and any one of tests rejects the null hypothesis that the pairs are 
independent of A and B gene. In this case, two independent hypotheses testing on the 
same data at 0.05 significance level may be instead of 0.025 (0.05/2). For different 
d-separated genes, we can get different significant p-value and so on.

On P.23 line 20-24 and P.24 line 1-2
According to the statistical network measure that we mentioned in section 3.4, we use 
the linear regression to calculate the straight line in a double logarithmic plot that 
shows the degree distribution against the number of links in Figure 9. While x-axis 
represents the log of the k links and y-axis represents the log of degree distribution. 
The linear fitting function of cancer network is $y = -5.5856x + 1.291$ with the 
correlation $R^2 = 0.9305$, otherwise, the normal network is $y = -2.2111x - 0.2769$ with the 
correlation $R^2 = 0.8931$.

On P.24 line 17-23
In Figure 10, we use the linear regression to calculate the straight line in a double 
logarithmic plot for the clustering coefficient against the number of links while x-axis 
represents the log of the k links and y-axis represents the log of clustering coefficient. 
The linear fitting function of the regulated network of a normal gene is $y = -1.0722x - 1.3964$ with the correlation $R^2 = 0.9103$. The linear fitting function of the 
regulated network of a cancer gene is $y = -1.1638x - 0.7922$ with the correlation 
$R^2 = 0.8291$. 
Table 6 - Number of links between two networks

<table>
<thead>
<tr>
<th>Links</th>
<th>Cancer</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial gene regulatory network (Before CI test)</td>
<td>15659</td>
<td>3765</td>
</tr>
<tr>
<td>Revised gene regulatory network (After CI test without Bonferroni correction)</td>
<td>8393</td>
<td>3497</td>
</tr>
<tr>
<td>Revised gene regulatory network (After CI test with Bonferroni correction)</td>
<td>8298</td>
<td>3497</td>
</tr>
<tr>
<td>Filter-out ratio</td>
<td>47%</td>
<td>7%</td>
</tr>
</tbody>
</table>
Table 8  - The parameter of degree distribution and clustering coefficient between normal and cancer

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>scaling exponent $s$</td>
<td>1.915916</td>
<td>2.120915</td>
</tr>
<tr>
<td>$\langle k \rangle$</td>
<td>2.71823</td>
<td>3.026623</td>
</tr>
<tr>
<td>$k_\infty$</td>
<td>1.465216</td>
<td>2.84916</td>
</tr>
<tr>
<td>Clustering coefficients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>scaling exponent $w$</td>
<td>-0.93048</td>
<td>-1.396294</td>
</tr>
<tr>
<td>$\langle C \rangle$</td>
<td>0</td>
<td>0.00576</td>
</tr>
</tbody>
</table>

Figure 12 Transcription regulator genes and their dependent genes which contain the activation interaction in cancer and the inhibition interaction in normal (Inside circle nodes denote transcription regulator genes and outside circle nodes denote dependent genes)

On P.28 line 4-6
See Additional file 12 shows the p-value of the independent test between the
transcription regulatory genes and their co-expressed genes with d-separated genes in figure 12 and 13.

Additional file 12 - the p-value of pair of genes involved in the figure 12 and 13

<table>
<thead>
<tr>
<th>TF</th>
<th>Co-expressed genes</th>
<th>P-value (cancer)</th>
<th>P-value (normal)</th>
<th>TF</th>
<th>Co-expressed genes</th>
<th>P-value (cancer)</th>
<th>P-value (normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUNX1</td>
<td>OSBPL6</td>
<td>0.009962</td>
<td>0.02940</td>
<td>CUTLI</td>
<td>RRB1P1</td>
<td>0.04300</td>
<td>0.042547</td>
</tr>
<tr>
<td>RUNX1</td>
<td>LETMD1</td>
<td>0.008547</td>
<td>0.011108</td>
<td>CUTLI</td>
<td>PEX10</td>
<td>0.00679</td>
<td>0.027149</td>
</tr>
<tr>
<td>RUNX1</td>
<td>ERCC2</td>
<td>0.001110</td>
<td>0.03423</td>
<td>CUTLI</td>
<td>IMP3</td>
<td>0.01045</td>
<td>0.042547</td>
</tr>
<tr>
<td>RELA</td>
<td>LPPR2</td>
<td>4.54473</td>
<td>0.03257</td>
<td>CUTLI</td>
<td>GSS</td>
<td>0.00740</td>
<td>0.042547</td>
</tr>
<tr>
<td>POU2F1</td>
<td>IQCE</td>
<td>0.00587</td>
<td>0.02426</td>
<td>CUTLI</td>
<td>BCAT2</td>
<td>1.01E-05</td>
<td>0.027149</td>
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<tr>
<td>POU2F1</td>
<td>DIO2</td>
<td>0.01349</td>
<td>0.04597</td>
<td>CUTLI</td>
<td>SCAMP2</td>
<td>0.03292</td>
<td>0.042547</td>
</tr>
<tr>
<td>NR3C1</td>
<td>CCNB3</td>
<td>7.93559E-4</td>
<td>0.03330</td>
<td>ATF2</td>
<td>SRP54</td>
<td>1.78387E-4</td>
<td>0.042158</td>
</tr>
<tr>
<td>NFYB</td>
<td>UBP1</td>
<td>8.84264E-7</td>
<td>0.03423</td>
<td>ATF2</td>
<td>SCAMP2</td>
<td>0.03931</td>
<td>0.042547</td>
</tr>
<tr>
<td>MYC</td>
<td>CDKN1C</td>
<td>1.40008E-91</td>
<td>0.01451</td>
<td>ATF2</td>
<td>SAA2</td>
<td>0.03616</td>
<td>0.037441</td>
</tr>
<tr>
<td>MAX</td>
<td>WASF2</td>
<td>0.00172</td>
<td>0.02435</td>
<td>ATF2</td>
<td>MOCS2</td>
<td>1.40794E-92</td>
<td>0.024158</td>
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<tr>
<td>MAX</td>
<td>MAP1A</td>
<td>0.00472</td>
<td>0.02963</td>
<td>ATF2</td>
<td>METTL4</td>
<td>0.00743</td>
<td>0.028129</td>
</tr>
<tr>
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<td>0.01604</td>
<td>ATF2</td>
<td>LRRC40</td>
<td>0.00509</td>
<td>0.042158</td>
</tr>
<tr>
<td>HSF2</td>
<td>PPP6C</td>
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<tr>
<td>HSF2</td>
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<td>0.02564</td>
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<td>ZNF161</td>
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<tr>
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<td>GNPAT</td>
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<td>0.00687</td>
<td>STAT1</td>
<td>PPP1R9A</td>
<td>0.00328</td>
<td>0.037425</td>
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<tr>
<td>HSF2</td>
<td>DLG4</td>
<td>0.00424</td>
<td>0.01278</td>
<td>STAT1</td>
<td>MAN2A1</td>
<td>0.01059</td>
<td>0.049536</td>
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</tbody>
</table>
**Table:**

<table>
<thead>
<tr>
<th>TF</th>
<th>Co-expressed genes</th>
<th>$d$-separated genes</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYC</td>
<td>CDKN1C</td>
<td>SP1</td>
<td>0.04</td>
</tr>
<tr>
<td>MAX</td>
<td>WASF2</td>
<td>ATF2</td>
<td>0.035</td>
</tr>
<tr>
<td>ATF2</td>
<td>SCAMP2</td>
<td>SP1</td>
<td>0.00288</td>
</tr>
<tr>
<td>MAX</td>
<td>MAPIA</td>
<td>ATF2</td>
<td>0.358</td>
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<tr>
<td>CUTL1</td>
<td>USF2</td>
<td>NFKB1</td>
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</tr>
<tr>
<td>SP1</td>
<td>RCP9</td>
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<td>0.039</td>
</tr>
</tbody>
</table>

**Figure 13** Transcription regulator genes and their dependent genes which contain the inhibition interaction in cancer and the activation interaction in normal (Inside circle nodes denote transcription regulator genes and outside circle nodes denote dependent genes)


### Additional file 12- the p-value of pair of genes involved in the figure 12 and 13

<table>
<thead>
<tr>
<th>TF</th>
<th>Co-expressed genes</th>
<th>P-value (cancer)</th>
<th>P-value (normal)</th>
<th>TF</th>
<th>Co-expressed genes</th>
<th>P-value (cancer)</th>
<th>P-value (normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUNX1</td>
<td>THBS2</td>
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<td>0.03742 5086</td>
<td>POU2F1</td>
<td>FCGR3A</td>
<td>0.001333</td>
<td>0.02539 607</td>
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<tr>
<td>RUNX1</td>
<td>SLIT2</td>
<td>0.00526 68615</td>
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<td>ZNF673</td>
<td>8.17E-06</td>
<td>4.05E-04</td>
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<td>RDH10</td>
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<td>ANKZF1</td>
<td>0.005743</td>
<td>0.01200 5</td>
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<tr>
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<td>0.00125 96726</td>
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<td>SULT1E1</td>
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<td>CPXM2</td>
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<td>GRLF1</td>
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<td>RXRA</td>
<td>0.381877 33</td>
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<td>RAN</td>
<td>0.03894 09</td>
<td>0.00201 517</td>
<td>YY1</td>
<td>CCND2BP 1</td>
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<td>0.00132 08861</td>
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<td>VPS4A</td>
<td>0.023298 99</td>
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<td>0.00729</td>
<td>0.02714</td>
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</table>
### TF Co-expressed genes d-separated genes P-value

<table>
<thead>
<tr>
<th>TF</th>
<th>Co-expressed genes</th>
<th>d-separated genes</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>HSF2</td>
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</table>

On P.28 line 6-7

Additional file 13 denotes the information of conditional independence testing results between without and with Bonferroni correction in cancer network.

Additional file 13: the part of conditional independence testing results between without and with Bonferroni correction

<table>
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<tr>
<th>Co-expressed genes</th>
<th>TF</th>
<th>d-separated genes</th>
<th>p-value</th>
<th>with Bonferroni correction</th>
<th>without Bonferroni correction (&lt;0.05)</th>
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<tr>
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<td>ATF2, E2F3</td>
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<tr>
<td>DCI</td>
<td>NFKB1</td>
<td>E2F3, STAT6</td>
<td>0.037146364</td>
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Q2: New results from DAVID and GSEA analysis indicate the proposed cancer network is involved in some critical biological functions and processes. While from my experience, it is not very common to identify so many extremely significant results from enrichment analysis, for example, p-value of 1.52E-68 after Bonferroni correction in supplementary files 4 and p-value of 2.57E-39 in supplementary files 5. The authors may need to double-check these p-values and provide the list of genes used for enrichment analysis so that the results in supplementary files 4, 5 and 6 can be repeated.

A1: Statistical hypothesis testing is in order to find significant evidence of gene regulation or d-separated genes and we use 2,283 dependent genes which are the co-expressed genes only affected by biomarkers (PBX1, EP300, STAT6, SREBF1, NFKB1, STAT3, EGR1, E2F3, NR2F2) and not exist in the normal network. In the previous manuscript, we use all GO functions such as cellular component, biological process and molecular functions to do the annotation and it may cause the smallest p-value of 1.52E-68 for significant enrichment results analysis of “GO:0005622~intracellular” which has large amount of genes belonging to this main category. Now, we only consider the results with significant pathways and biological process annotation using DAVID toolkit in Additional file 4 and we also consider the same gene sets to the enrichment pathway from GSEA online tool which is calculated by hypergeometric distribution method. The following screenshot (1) denotes 2,110 genes with functional annotation clustering by DAVID toolkit and screenshot (2) denotes the 2,259 genes computing their overlap pathways by GSEA toolkit. Although there still some extremely p-value such as 2.28E-20 in Additional file 4, those categories are top category which is near the root node in GO structure and large number of genes involved in the category. For example, there are 3,789 genes are belonging to the “primary metabolic process” category in GO annotation of human species. We present the complete significant biological processes results annotated by DAVIS and manually pick regulation of progression through cell differentiation, cell death, I-kappaB kinase/NF-kappaB cascade, vesicle-mediated transport, apoptosis as important biological functions and processes which are more specific categories. The other reason for extremely p-value using GSEA toolkit may be dependent on the large number of test genes and let the denominator of hypergeometric function larger but the smaller p-value still means significant.
Screenshot (1) of functional annotation clustering using DAVID toolkit

Screenshot (2) of computing overlap pathways using GSEA toolkit
On P.26 line 23-24 and P.27 line 1-8
We take 2,283 dependent genes see Additional file 14 affected by biomarkers (PBX1, EP300, STAT6, SREBF1, NFKB1, STAT3, EGR1, E2F3, NR2F2) and not exist in normal network to do the functional annotation using DAVID online toolkit and there are 2,110 genes can be annotated in DAVID toolkit. We filtered the results at least 3 members in each functional category and P-value<0.05 with Bonferroni correction and FDR<0.25 see Additional file 4. The functional annotation clustering results show that the cancer networks are associated with regulation of progression through cell differentiation, cell death, I-kappaB kinase/NF-kappaB cascade, vesicle-mediated transport, apoptosis biological functions and processes.

Additional file 14 – 2,283 test genes for DAVID and GSEA toolkit

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On P.27 from line 8-16

We also consider performing the pathway enrichment from GSEA online tool which is calculated by hypergeometric distribution method and there are 2,259 genes can be annotated in GSEA online tool. We filtered the indeed functional enrichment canonical pathways from the gene set in our networks with at least 3 members in each functional category and P-value<0.05. The results denote cell adhesion molecules, androgen and estrogen metabolism, smooth muscle contraction and some GO annotated pathways see Additional file 5. The genes in the cancer network are involved in the significant pathways such as Toll like receptor, PPAR, ERBB, P53 and WNT signaling pathway see Additional file 6.

Additional file 5- the enrichment canonical pathways and their p-values in cancer network

<table>
<thead>
<tr>
<th>Term name</th>
<th>p-value</th>
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<td>HSA04080_NEUROACTIVE_LIGAND_RECEPTOR_INTERACTION</td>
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<td>HSA04080_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION</td>
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<td>HSA04810_REGULATION_OF_ACTIN_CYTOSKELETON</td>
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<td>HSA01430_CELL_COMMUNICATION</td>
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<td>HSA04010_MAPK_SIGNALING_PATHWAY</td>
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<td>HSA04510_FOCAL_ADHESION</td>
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<td>HSA04514_CELL_ADHESION_MOLECULES</td>
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<td>HSA01030_GLYCAN_STRUCTURES_BIOSYNTHESIS_1</td>
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<td>HSA04630_JAK_STAT_SIGNALING_PATHWAY</td>
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<td>HSA04360_AXON_GUIDANCE</td>
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<td>HSA04670_LEUKOCYTE_TRANSENDOTHELIAL_MIGRATION</td>
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<td>HSA04530_TIGHT_JUNCTION</td>
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<td>HSA04640HEMEPOPOETIC_CELL_LINEAGE</td>
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<td>SMOOTH_MUSCLE_CONTRACTION</td>
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<td>HSA04512_ECM_RECEPTOR_INTERACTION</td>
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Additional file 6- The genes are belong to the enrichment canonical pathways in cancer network

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<th>Geneset name</th>
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<td>HSA04514_CELL_ADHESION_MOLECULES</td>
<td>CD40, F11R, JAM3, ESAM, HLA-DMB, HLA-DPA1, HLA-DPB1, HLA-DQB2, PVRL3, CNTNAP1, GLG1, NRXN2</td>
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<td>SMOOTH_MUSCLE_CONTRACTION</td>
<td>EDG2, PRKACB, NFKB1, ATF2, CAMK2D,</td>
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<td>HSA03320_PPAR_SIGNALING_PATHWAY</td>
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<td>HSA04115_P53_SIGNALING_PATHWAY</td>
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