TCGA Clear Cell Renal Cell Carcinoma Project

TCGA KIRC AWG

Co-Chairs: Richard Gibbs, Marston Linehan
Data Coordinator: Maggie Morgan
Analysis Coordinators: Chad Creighton, Roel Verhaak
Writing team: Marston Linehan, W. Kim Rathmell, Chad Creighton, Roel Verhaak, Richard Gibbs
Background

• Genetic changes underlying clear cell renal cell carcinoma (ccRCC) include alterations in genes controlling cellular oxygen sensing (e.g. \textit{VHL}) and the maintenance of chromatin states (e.g. \textit{PBRM1}).

• For 446 ccRCC cases, TCGA evaluated clinical and pathological features, genomic alterations, DNA methylation profiles, and RNA and proteomic signatures.
## Data summary

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<td>Total Cases</td>
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Significantly mutated genes

372 ccRCC tumor samples

Verhaak R, Wheeler D, TCGA
Somatic mutations called by three centers

Poster #114  Howe C, Liu X, Chang K, Wheeler D, TCGA
Corresponding validation rates

Poster #114  Howe C, Liu X, Chang K, Wheeler D, TCGA
Significantly mutated genes

372 ccRCC tumor samples

Frequent VHL alterations
(91% copy, 55% mutation, 7% methylation)

Verhaak R, Wheeler D, TCGA
Significantly mutated genes

372 ccRCC tumor samples

Mutations in chromatin regulators PBRM1, SETD2, BAP1, ARID1A

Verhaak R, Wheeler D, TCGA
Significantly mutated genes

372 ccRCC tumor samples

Mutations in PI3K pathway regulators

Verhaak R, Wheeler D, TCGA
Copy number alterations

VHL
PBRM1
SETD2
BAP1

R Beroukhim,
S Signoretti,
TCGA
Copy number alterations

Significance of focal SCNAs

Deletions

1p36.13
NEGR1 (1)
1p31.1
2q37.1
VHL (118)
PBRM1 (4)
3p14.3
FHIT (7)
3p14.2
3p14.1
3p12.3
3p12.3
3q11.2
4q35.2
QKI (1)
PTPRD (1)
CDKN2A (2)
PTEN (2)
10q26.2
15q21.1

Amplifications

1q21.3
MDM4 (14)
2q33.1
3p26.3
PRKCI/TERC (16)
4q32.1
5q15
5q21.1
5q35.3
7q11.22
7q36.3
MYC (191)
JAK2 (1)

14q13.1
IDH2 (20)
17q12
17q25.3
Xq12
Xq28

R Beroukhim,
S Signoretti,
TCGA
Recurrent fusion RNA transcripts

R Verhaak,
W Torres-Garcia,
TCGA
Widespread DNA hypomethylation associated with mutation of SETD2

Shen H, Laird P, TCGA
DNA hypermethylation increases with advancing tumor stage and grade

Shen H, Laird P, TCGA
Mutations involving the SWI/SNF chromatin remodeling complex show far-reaching effects on other pathways.

Paull E, Stuart J, Raphael B, TCGA
Mutations involving the SWI/SNF chromatin remodeling complex show far-reaching effects on other pathways.

Paull E, Stuart J, Raphael B, TCGA
Molecular signatures and pathways of aggressive ccRCC
A gene expression signature of survival in high grade serous ovarian cancer

- Defined using a training dataset
- Applied to multiple test datasets in predicting higher risk versus lower risk patients

Creighton CJ and TCGA consortium, Nature 2011
A gene expression signature of survival in high grade serous ovarian cancer

Creighton CJ and TCGA consortium, Nature 2011
Molecular signatures of survival in ccRCC

<table>
<thead>
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Creighton CJ and TCGA consortium
Molecular signatures of survival in ccRCC

Creighton CJ and TCGA consortium
Protein survival correlates in ccRCC include AMPK and acetyl-CoA carboxylase.

LOW AMPK, HIGH acetyl-coA carboxylase = worse outcome

AMPK → Acetyl-coA carboxylase → aerobic glycolysis
Survival correlates underlie a glycolytic shift

Creighton CJ, Linehan WM, Ricketts C, TCGA
Survival correlates underlie a glycolytic shift

Creighton CJ, Linehan WM, Ricketts C, TCGA
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Creighton CJ, Linehan WM, Ricketts C, TCGA
Survival correlates underlie a glycolytic shift

Creighton CJ, Linehan WM, Ricketts C, TCGA
The PI3K pathway is highly targeted at the genetic and genomic levels

Anderson J, Ciriello G, Schultz N, Sander C, TCGA
Promoter methylation of miR-21 and **GRB10** contributes to PI3K pathway deregulation

Creighton CJ, Robertson AG, Laird P, TCGA

Survival correlation
- Worse outcome
- Better outcome

RNA  protein  meth.
Promoter methylation of miR-21 and **GRB10** contributes to PI3K pathway deregulation.

**Survival correlation**
- Worse outcome
- Better outcome

**miR21 meth**
- **miR21 expr**
- **PTEN expr**
Promoter methylation of miR-21 and GRB10 contributes to PI3K pathway deregulation

GRB10 meth
GRB10 expr
PI3K activity

Survival correlation
Worse outcome
Better outcome

RNA
protein
meth.
Conclusions

• Integrative analyses highlights the importance of both VHL/HIF pathway and chromatin remodeling/histone methylation pathway

• Frequent targeting of PI3K pathway at genetic, genomic, and epigenetic levels

• A metabolic shift to aerobic glycolysis appears involved with more aggressive disease
# Kidney Cancer Disease Working Group

(apologies for any omissions)

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Richard Gibbs</td>
<td>Baylor</td>
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<tr>
<td>(co-chair)</td>
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<td>Marston Linehan</td>
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STAFF: Kenna Shaw, Margi Sheth, Lindsay Lund, + NCI Senior Leadership; Brad Ozenberger, Peter Good, Jacqueline Palchik + NHGRI Senior Leadership