

Comprehensive molecular characterization of clear cell renal cell carcinoma

The Cancer Genome Atlas Research Network

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Abstract

Genetic changes underlying clear cell renal cell carcinoma (ccRCC) include alterations in genes controlling cellular oxygen sensing (for example, *VHL*) and the maintenance of chromatin states (for example, *PBRM1*). We surveyed more than 400 tumours using different genomic platforms and identified 19 significantly mutated genes. The PI(3)K/AKT pathway was recurrently mutated, suggesting this pathway as a potential therapeutic target. Widespread DNA hypomethylation was associated with mutation of the H3K36 methyltransferase *SETD2*, and integrative analysis suggested that mutations involving the SWI/SNF chromatin remodelling complex (*PBRM1*, *ARID1A*, *SMARCA4*) could have far-reaching effects on other pathways. Aggressive cancers demonstrated evidence of a metabolic shift, involving downregulation of genes involved in the TCA cycle, decreased AMPK and PTEN protein levels, upregulation of the pentose phosphate pathway and the glutamine transporter genes, increased acetyl-CoA carboxylase protein, and altered promoter methylation of miR-21 (also known as *MIR21*) and *GRB10*. Remodelling cellular metabolism thus constitutes a recurrent pattern in ccRCC that correlates with tumour stage and severity and offers new views on the opportunities for disease treatment.

Introduction

Kidney cancers, or renal cell carcinomas (RCC), are a common group of chemotherapy-resistant diseases that can be distinguished by histopathological features and underlying gene mutations¹. Inherited predisposition to RCC has been shown to arise from genes involved in regulating cellular metabolism, making RCC a model for the role of an oncologic-metabolic shift, commonly referred to as the 'Warburg effect', leading to malignancy². The most common type of RCC, clear cell renal cell carcinoma (ccRCC), is closely associated with *VHL* gene mutations that lead to stabilization of hypoxia inducible factors (*HIF-1 α* and *HIF-2 α* , also known as *HIF1A* and *EPAS1*) in both sporadic and familial forms. *PBRM1*, a subunit of the PBAF SWI/SNF chromatin remodelling complex, as well as histone deubiquitinase *BAP1* and histone methyltransferase *SETD2*, were recently found to be altered in ccRCC^{3,4,5}, implicating major roles for epigenetic regulation of additional functional pathways participating in the development and progression of the disease. Oncogenic metabolism and epigenetic reprogramming have thus emerged as central features of ccRCC.

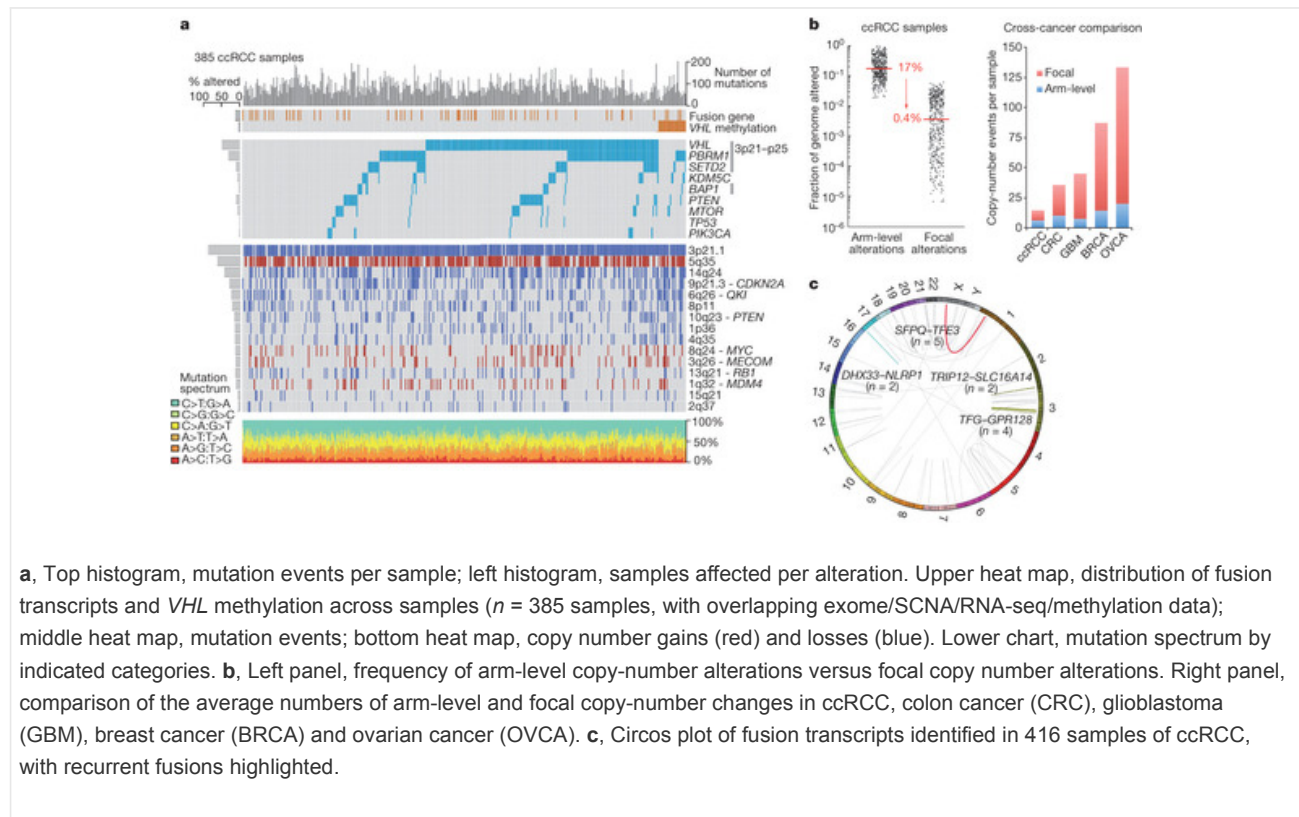
In the present study, clinical and pathological features, genomic alterations, DNA methylation profiles, and RNA and proteomic signatures were evaluated in ccRCC. We accrued more than 500 primary nephrectomy specimens from patients with histologically confirmed ccRCC that conformed to the requirements for genomic study defined by the Cancer Genome Atlas (TCGA), together with matching 'normal' genomic material. Samples were restricted to those that contained at least 60% tumour nuclei (median 85%) by pathological review (clinical data summary provided in Supplementary Table 1). A data freeze representing 446 samples was generated from at least one analytical platform ('Extended' data set) and data from all platforms were available for 372 samples for coordinated, integrative analyses ('Core' data set) (Supplementary Data 1,

Supplementary Table 2). No substantial batch effects in the data that might confound analyses were detected (Supplementary Figs 1–20).

Somatic alterations

The global pattern of somatic alterations, determined from analysis of 417 samples, is shown in Fig. 1a. DNA hybridizations showed that recurrent arm-level and focal somatic copy number alterations (SCNAs) occurred at a fewer sites than is generally observed in other cancers ($P < 0.0004$; Supplementary Figs 21–22 and Supplementary Table 3). However, SCNAs that were observed more commonly involved entire chromosomes or chromosome arms, rather than focal events (17% vs 0.4%, Fig. 1b). Notably, the most frequent arm-level events involved loss of chromosome 3p (ref. 6; 91% of samples), encompassing all of the four most commonly mutated genes (*VHL*, *PBRM1*, *BAP1* and *SETD2*).

Figure 1: Somatic alterations in ccRCC.



The data also suggested lower and more variable tumour cellularity⁷ in the accrued samples, compared to conventional pathological review (median $54\% \pm 14\%$). This may reflect stromal or endothelial cell contributions, or tumour cell heterogeneity. A recent study of multiple samples from single tumours has demonstrated significant regional genomic heterogeneity, but with shared mutations in frequently mutated genes and convergent evolution of other common gene level events⁸. The mutation frequencies of key genes (*VHL*, *PBRM1* and so on), as well as copy number gains and losses found here, were, however, consistent with previous reports. Tumour purity was therefore not determined to be a limitation in the current study.

Arm level losses on chromosome 14q, associated with loss of *HIF1A*, which has been predicted to drive more aggressive disease⁹, were also frequent (45% of samples). Gains of 5q were observed (67% of samples) and additional focal amplifications refined the region of interest to 60 genes in 5q35, which was particularly informative as little has been known about the importance of this region in ccRCC since the 5q gain was initially described. Focal amplification also implicated the protein kinase C member *PRKCI* (ref. 10), and the MDS1 and EVI1 complex locus *MECOM* at 3p26, the p53 regulator *MDM4*

at 1q32, *MYC* at 8q24 and *JAK2* on 9p24. Focally deleted regions included the tumour suppressor genes *CDKN2A* at 9p21 and *PTEN* at 10q23, putative tumour suppressor genes *NEGR1* at 1p31, *QKI* at 6q26, and *CADM2* at 3p12 and the genes that are frequently deleted in cancer, *PTPRD* at 9p23 and *NRXN3* at 14q24 (ref. 11).

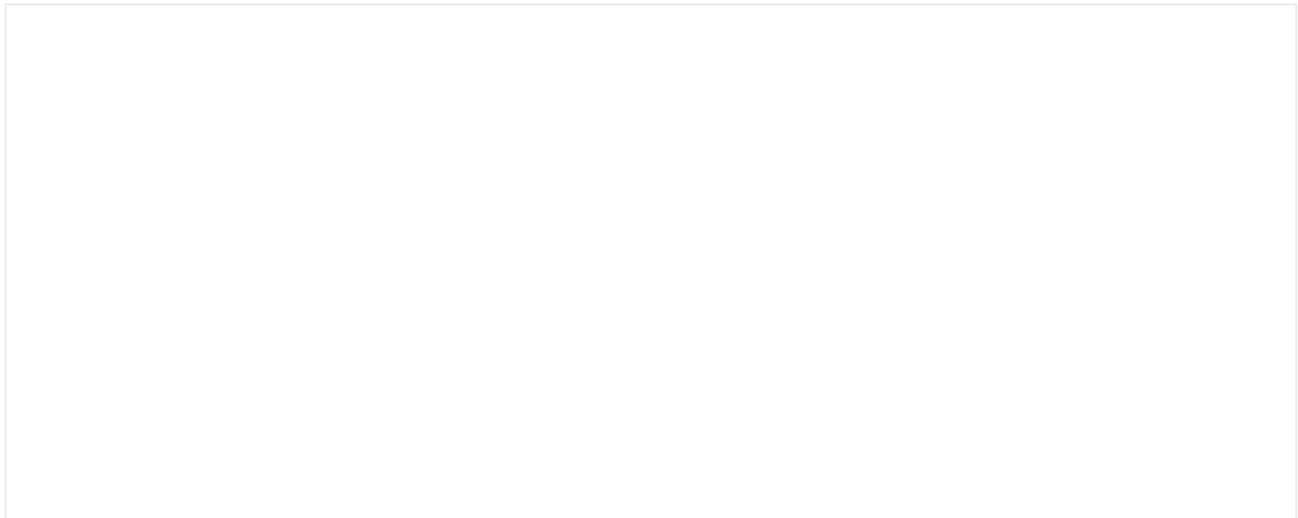
Whole-exome sequencing (WES) of tumours from 417 patients identified 36,353 putative somatic mutations, including 16,821 missense mutations, 6,383 silent mutations and 2,999 indels, with an average of 1.1 ± 0.5 non-silent mutations per megabase (Supplementary Figs 23–25). Mutations from 50 genes with high apparent somatic mutation frequencies (Supplementary Table 4) were independently validated using alternative sequencing instrumentation (Supplementary Fig. 26). In tumours from 22 patients, whole-genome sequencing was also used to validate and calibrate the WES data and confirmed 83% of the WES mutation-calls (Supplementary Tables 5 and 6). In line with results of previous studies (Supplementary Tables 7 and 8), the validated mutation data identified nineteen significantly mutated genes (SMGs) (false discovery rate (FDR) < 0.1), with *VHL*, *PBRM1*, *SETD2*, *KDM5C*, *PTEN*, *BAP1*, *MTOR* and *TP53* representing the eight most extreme members ($q < 0.00001$) (Fig. 1a). Eleven additional SMGs were of considerably lower significance ($q < 0.1–0.5$) but included known cancer genes. Among all SMGs, only mutation of *BAP1* correlated with poor survival outcome (Supplementary Fig. 27)¹². Approximately 20% of cases had none of the 19 recorded SMGs, although many contained rare mutations in other known oncogenes or tumour suppressors, involving survival associations, illustrating the genetic complexity of ccRCC⁸ (Supplementary Figs 28–30 and Supplementary Table 9).

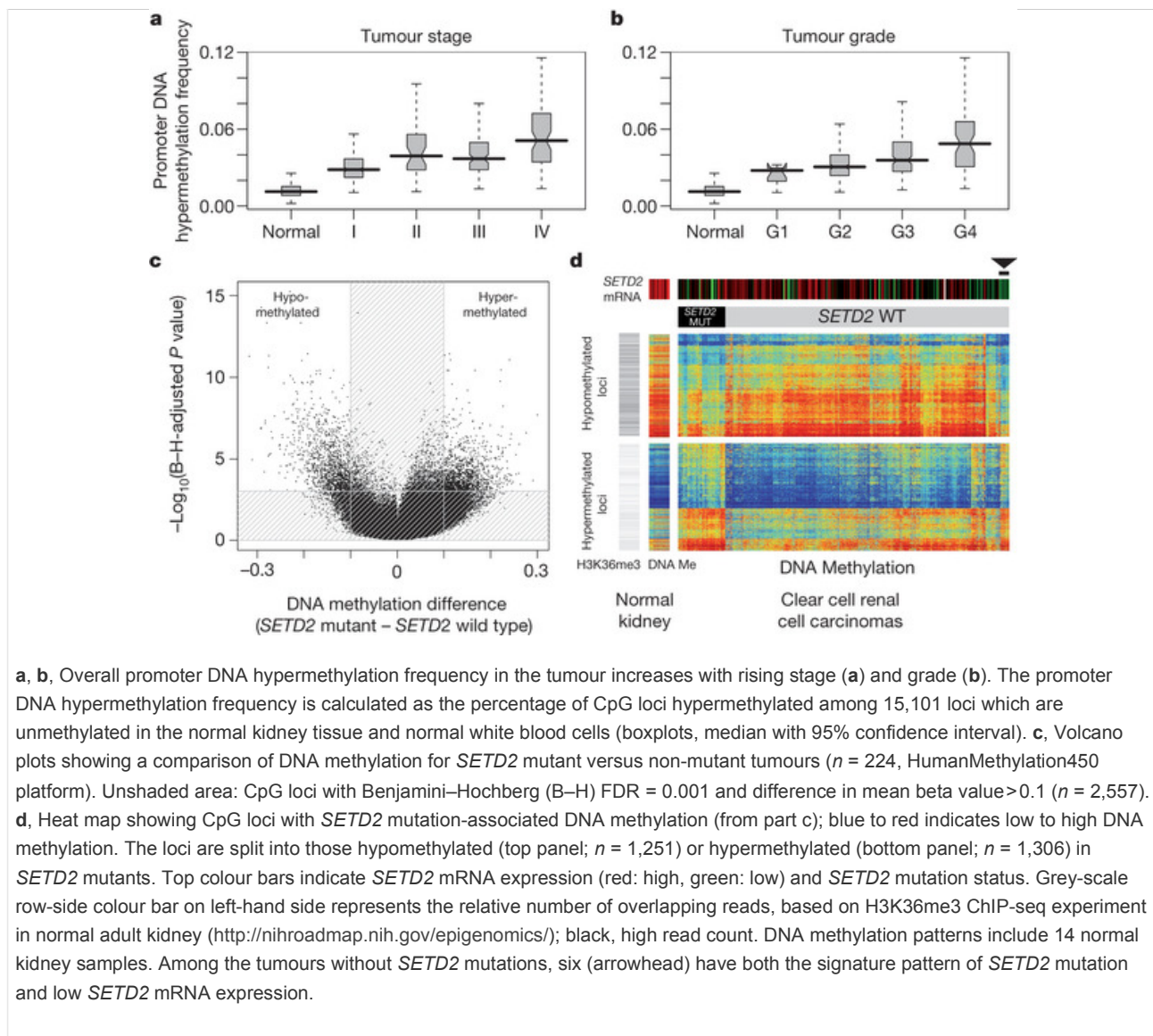
Eighty-four putative RNA fusions were identified in 416 ccRCC samples¹³. Eleven of thirteen predicted events (Fig. 1c) were validated using targeted methods, consistent with an 85% true-positive rate (Supplementary Table 10 and Supplementary Figs 31–35). A recurrent *SFPQ–TFE3* fusion (previously linked to non-clear cell translocation-associated RCC¹⁴) was found in five samples, all of which were *VHL* wild type, indicating either that these tumours are a clear cell variant or that translocation-associated renal tumours may be histologically indistinguishable from conventional ccRCC. Furthermore, the TFE3 protein as well as an X(p11) rearrangement was found in three of those samples, where there were available slides.

DNA methylation profiles

We observed epigenetic silencing of *VHL* in about 7% of ccRCC tumours, which was mutually exclusive with mutation of *VHL* (Fig. 1a), reflecting the central role of this locus in ccRCC¹⁵. An additional 289 genes showed evidence of epigenetic silencing in at least 5% of tumours. The top-ranked gene by inverse correlation between gene expression and DNA methylation was *UQCRH*, hypermethylated in 36% of the tumours. *UQCRH* has been previously suggested to be a tumour suppressor¹⁶, but not linked to ccRCC. Interestingly, increasing promoter hypermethylation frequency correlated with higher stage and grade (Fig. 2a, b).

Figure 2: DNA methylation and ccRCC.



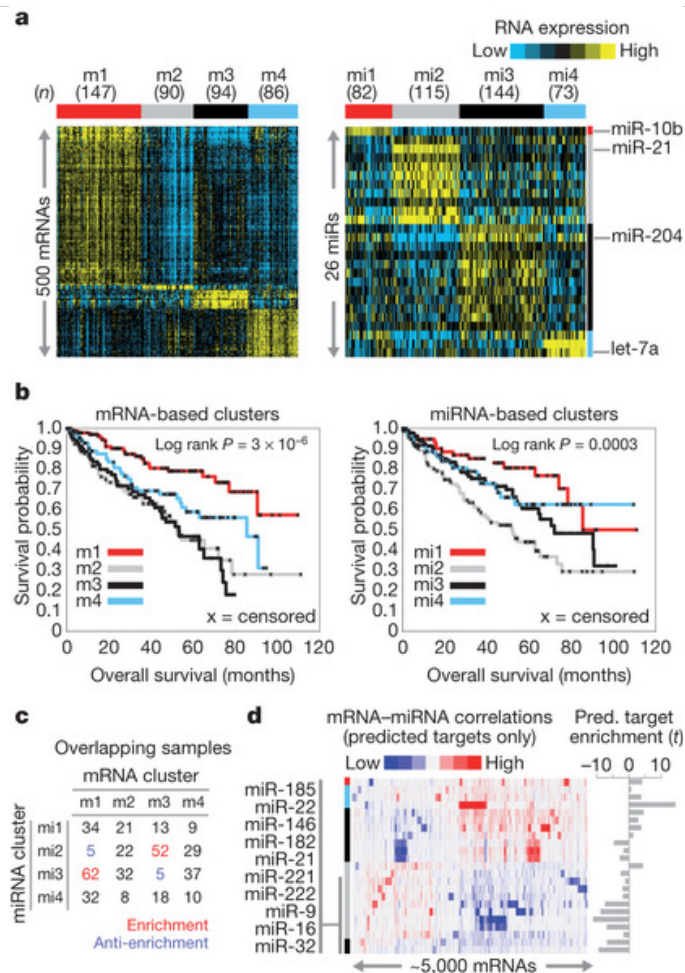


We also evaluated the global consequences of mutation in specific epigenetic modifiers. Mutations in *SETD2*, a non-redundant H3K36 methyltransferase, were associated with increased loss of DNA methylation at non-promoter regions (Fig. 2c, d). This discovery is consistent with the emerging view that H3K36 trimethylation may be involved in the maintenance of a heterochromatic state¹⁷, whereby DNA methyltransferase 3A (DNMT3A) binds H3K36me3 and methylates nearby DNA¹⁸. Thus, reductions of H3K36me3 through *SETD2* inactivation could lead indirectly to regional loss of DNA methylation.

RNA expression

Unsupervised clustering methods identified four stable subsets in both mRNA (m1–m4) and miRNA (mi1–mi4) expression data sets (Fig. 3a and Supplementary Figs 36–39). Supervised clustering revealed the similarity of these new mRNA classes to the previously reported ccA and ccB expression subtypes¹⁹, with cluster m1 corresponding to ccA and ccB divided between m2 and m3 (Supplementary Table 11). Cluster m4 probably accounts for the roughly 15% of tumours previously unclassified in the ccA/ccB classification scheme. Similarly, the survival advantage previously observed for ccA cases was again identified for m1 tumours (Fig. 3b).

Figure 3: mRNA and miRNA patterns reflect molecular subtypes of ccRCC.



a, Tumours were separated into four sample groups (that is, 'clusters') by unsupervised analyses, on the basis of either differentially expressed mRNA patterns (left panel, showing 500 representative genes: m1–m4) or differentially expressed miRNA patterns (right panel, showing 26 representative miRNAs: mi1–mi4). **b**, Significant differences in patient survival were identified for both the mRNA-based clusters (left panel) and the miRNA-based clusters (right panel). **c**, Numbers of samples overlapping between the two sets of clusters, with significant concordance observed between m1 and mi3 and between m3 and mi2; red, significant overlap ($P < 10^{-5}$, chi-squared test). **d**, mRNA–miRNA correlations, for predicted targeting interactions. Rows indicate miRNAs from **a** (indicated by cluster-specific colour bar); columns, mRNAs (5,000 differentially regulated genes selected for average RPKM > 10 and at least one predicted miRNA interaction); mRNA–miRNA entries with no predicted targeting are white. To the right of the correlation matrix, t statistics (Spearman's rank) indicate group target enrichment.

The m1 subtype was characterized by gene sets associated with chromatin remodelling processes and a higher frequency of *PBRM1* mutations (39% in m1 vs 27% in others, $P = 0.027$). Deletion of *CDKN2A* (53% vs 26%; $P < 0.0001$) and mutations in *PTEN* (11% vs 1%; $P < 0.0001$) were more frequent in m3 tumours (Supplementary Fig. 5). The m4 group showed higher frequencies of *BAP1* mutations (17% vs 7%; $P = 0.002$) and base-excision repair; however, this group also harboured more *mTOR* mutations (12% vs 4%; $P = 0.01$) and ribosomal gene sets.

Survival differences evident in miRNA-based subtypes (Supplementary Figs 40–44) correlated with the mRNA data (Fig. 3b–d). For example, miR-21, previously shown to demonstrate strong regulatory interactions in ccRCC²⁰ and with established roles in metabolism^{17, 21, 22} correlated strongly with worse outcome, and DNA promoter methylation levels inversely correlated with expression of miR-21, miR-10b and miR-30a (Supplementary Tables 12–14). miRNA interactions thus represent a significant component of the epigenetic regulation observed in ccRCC.

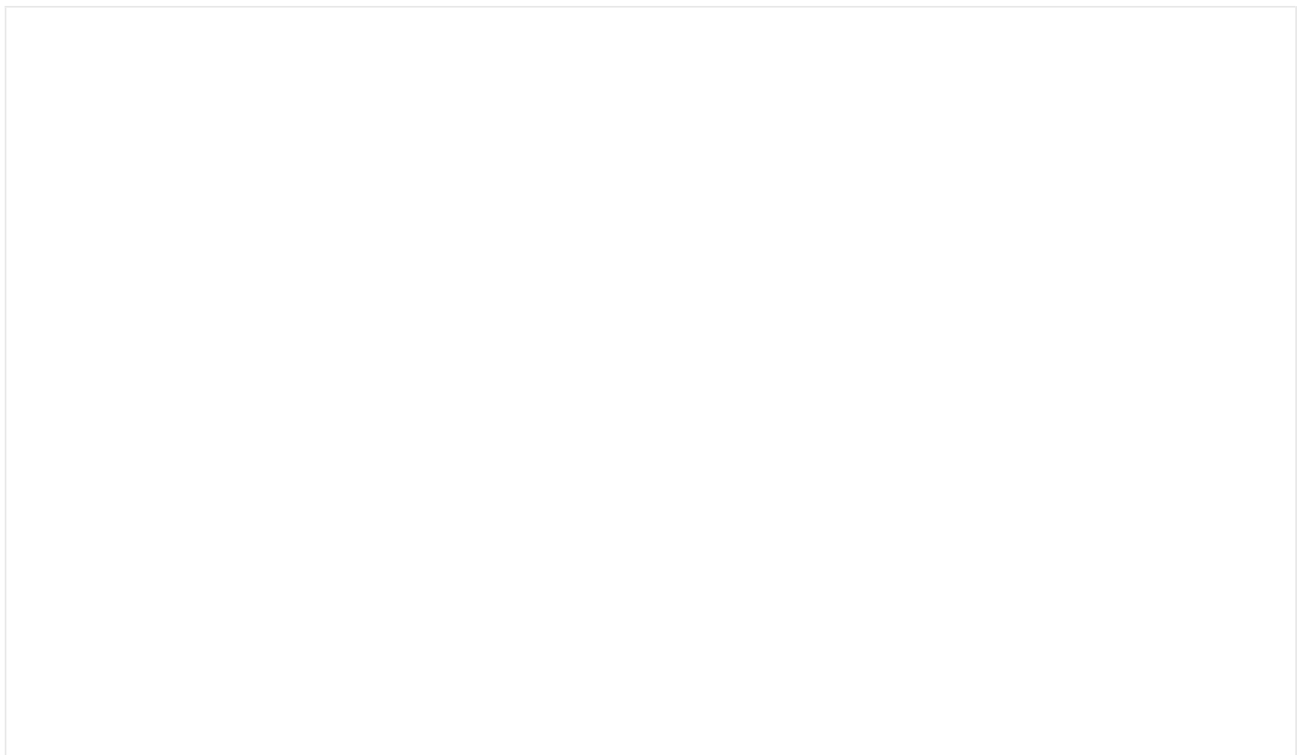
Integrative data analyses

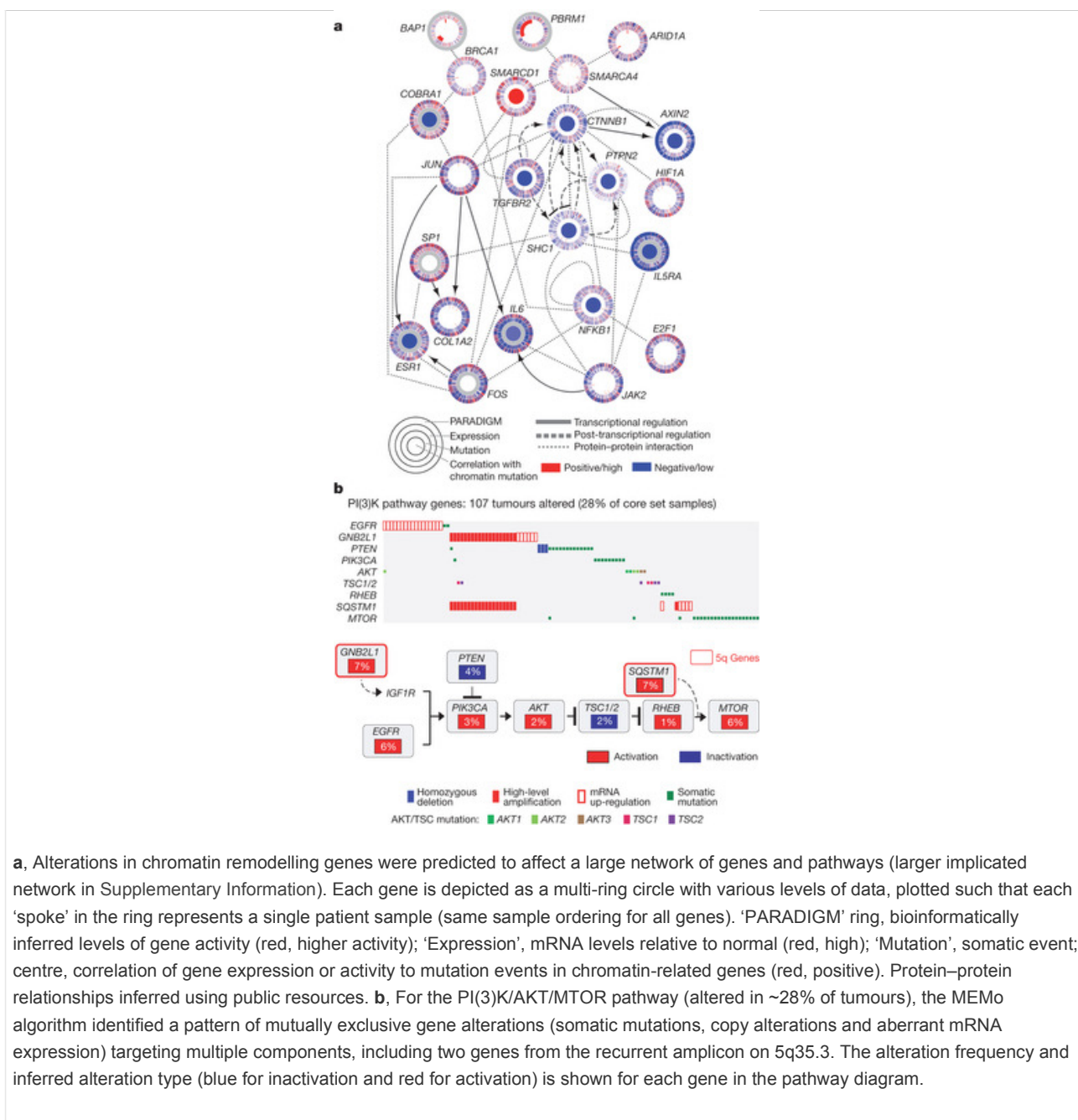
We used a combination of approaches for integrative pathway analysis. The HotNet²³ algorithm uses a heat diffusion model, to find sub-networks distinguished by both the frequency of mutation in genes (nodes in the network) and the topology of interactions between genes (edges in the network). In ccRCC, HotNet identified twenty-five sub-networks of genes within a genome-scale protein–protein interaction network (Supplementary Table 15 and Supplementary Fig. 45). The largest and most frequently mutated network contained *VHL* and interacting partners. The second most frequently mutated sub-network included *PBRM1*, *ARID1A* and *SMARCA4*, key genes in the PBAF *SWI/SNF* chromatin remodelling complex.

We also inferred activities for known pathways, by using the PARADIGM algorithm to incorporate mutation, copy and mRNA expression data, with pathway information catalogued in public databases. This method identified a highly significant sub-network of 2,398 known regulatory interactions, connecting 1,218 molecular features (645 distinct proteins) (Supplementary Figs 46–49 and Supplementary Tables 16 and 17). Several ‘active’ transcriptional ‘hubs’ were identified, by searching for transcription factors with targets that were inferred to be active in the PARADIGM network. The active hubs found included HIF1A/ARNT, the transcription factor program activated by *VHL* mutation, as well as MYC/MAX, SP1, FOXM1, JUN and FOS. These hubs, together with several other less well-studied transcription factors, interlink much of the transcriptional program promoting glycolytic shift, de-differentiation and growth promotion in ccRCC.

We next searched for causal regulatory interactions connecting ccRCC somatic mutations to these transcriptional hubs, using a bi-directional extension to HotNet (‘TieDIE’) and identified a chromatin-specific sub-network (Fig. 4a and Supplementary Figs 50–52). TieDIE defines a set of transcriptional targets, whose state in the tumour cells is proposed to be influenced by one or more of the significantly mutated genes. The chromatin modification pathway intersects a wide variety of processes, including the regulation of hormone receptors (for example, *ESR1*), RAS signalling via the *SRC* homologue (*SHC1*), immune-related signalling (for example, *NFKB1* and *IL6*)²⁴, transcriptional output (for example, *HIF1A*, *JUN*, *FOS* and *SP1*), DNA repair (via *BAP1*) and beta-catenin (*CTNNB1*) and transforming growth factor (TGF)- β (*TGFBR2*) signalling via interactions with a *SMARC–PBRM1–ARID1A* complex. The complexity of these interactions reflects the potential for highly pleiotropic effects following primary events in chromatin modification genes.

Figure 4: Genomically-altered pathways in ccRCC.





The mutations in the chromatin regulators *PBRM1*, *BAP1* and *SETD2* were differentially associated with altered expression patterns of large numbers of genes when compared to samples bearing a background of *VHL* mutation (Supplementary Tables 18–21 and Supplementary Fig. 53). Each chromatin regulator had a distinct set of downstream effects, reflecting diverse roles for chromatin remodelling in the transcriptome.

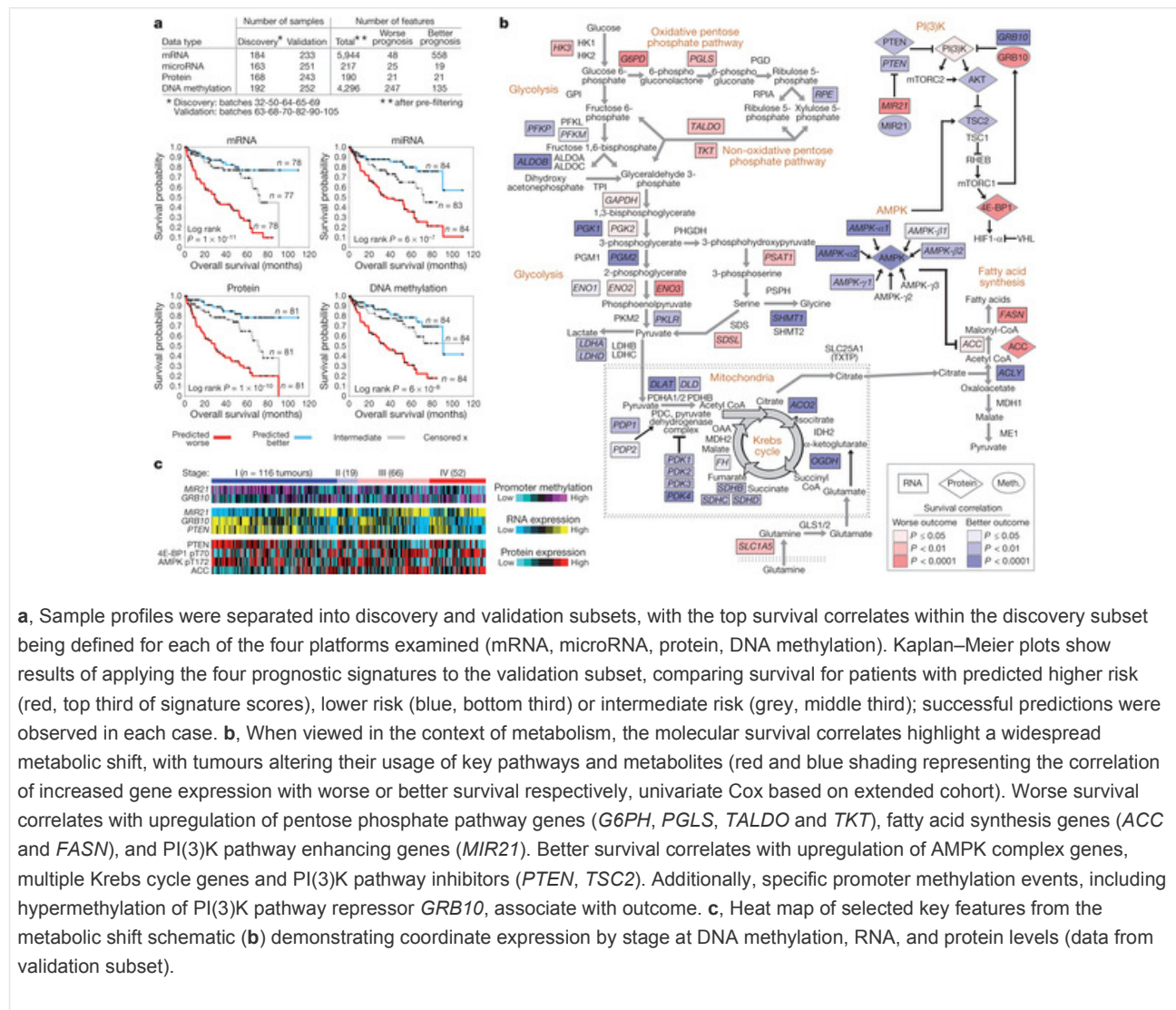
Additionally, an unsupervised pathway analysis using the MEMO algorithm²⁵ identified mutually exclusive patterns of alterations targeting multiple components of the PI(3)K/AKT/MTOR pathway in 28% of the tumours (Fig. 4b and Supplementary Table 22). Interestingly, the altered gene module included two genes from the broad amplicon on 5q35.3: *GNB2L1* and *SQSTM1*. Both these genes have previously been associated with activation of PI(3)K signalling^{26, 27}. Furthermore, mRNA expression levels of these two genes were correlated with both DNA copy number increases and alteration status of the PI(3)K pathway (Supplementary Figs 54–55). The mutual exclusivity module also includes frequent

overexpression of EGFR, which correlates with increased phosphorylation of the receptor (Supplementary Fig. 56), and which has been previously associated with lapatinib response in ccRCC²⁸.

Correlations with survival

Where unsupervised analyses had indicated that common molecular patterns were associated with patient survival, we sought to further define molecular prognostic signatures at the levels of mRNA, miRNA, DNA methylation and protein. Data were divided into 'discovery' ($n = 193$) and 'validation' ($n = 253$) sets and platform-specific signatures were defined using Cox analyses²⁴. Kaplan–Meier analysis for each signature showed statistically significant associations with survival in the validation subset (Fig. 5a and Supplementary Fig. 57). Multivariate Cox analyses, incorporating established clinical variables, showed that the mRNA, miRNA and protein signatures provided additional prognostic power (Supplementary Table 23). In addition, these signatures could provide molecular clues as to the drivers of aggressive cancers.

Figure 5: Molecular correlates of patient survival involve metabolic pathways.



Top protein correlates of worse survival included reduced AMP-activated kinase (AMPK) and increased acetyl-CoA carboxylase (ACC) (Supplementary Fig. 58). Together, downregulation of AMPK and upregulation of ACC activity contribute to a metabolic shift towards increased fatty acid synthesis²⁹. A metabolic shift to an altered use of key metabolites and pathways was also apparent when considering the full set of genes involved in the core metabolic processes, including a shift

towards a 'Warburg effect'-like state (Fig. 5b). Poor prognosis correlated with downregulation of AMPK complex and the Krebs cycle genes, and with upregulation of genes involved in the pentose phosphate pathway (*G6PD*, *PGLS*, *TALDO* (also known as *TALDO1P1*), *TKT*) and fatty acid synthesis (*FASN*, *ACC* (also known as *ACACA*)).

Examination of potential genetic or epigenetic drivers of a glycolytic shift led us to identify methylation events involving *MIR21* and *GRB10*, with decreased promoter methylation of each gene (thereby higher expression) being associated with worse or better outcome, respectively (Fig. 5b, Supplementary Fig. 59 and Supplementary Table 24). Both genes regulate the PI(3)K pathway: *miR-21* is inducible by high glucose levels and downregulates PTEN²²; whereas the tumour suppressor *GRB10* negatively regulates PI(3)K and insulin signalling³⁰. Promoter methylation of *MIR21* and *GRB10* were coordinated with their mRNA expression patterns, as well as with the mRNA expression of other key genes and protein expression in the metabolic pathways (Fig. 5c and Supplementary Fig. 60). In addition to the PI(3)K pathway (Fig. 5b and Supplementary Fig. 61), molecular survival correlations involved several pro-metastatic matrix metalloproteinases (Supplementary Fig. 62).

Discussion

Our study sampled a single site of the primary tumour, in a disease with a potentially high level of tumour heterogeneity⁸. The extent to which convergent evolutionary events are a common theme in ccRCC remains to be determined, but may indicate that critical genes will be represented across the tumour landscape for an individual mass. In general, the large sample size seemed to overcome the intrinsic challenges of studying a genetically complex disease, revealing rare variants at rates similar to what has been described previously³. The samples, taken from primary tumour specimens, were reflective of patients fit for either definitive or cytoreductive nephrectomy, whereas future work could explore the genomic landscape of metastatic lesions.

Pathway and integrated analyses highlighted the importance of the well-known VHL/HIF pathway, the newly emerging chromatin remodelling/histone methylation pathway, and the PI(3)K/AKT pathway. The observation of chromatin modifier genes being frequently mutated in ccRCC strongly supports the model of nucleosome dynamics, providing a key function in renal tumorigenesis. Although the mechanistic details remain to be defined as to how such modulation promotes tumour formation, the data presented here revealed alterations in DNA methylation associated with *SETD2* mutations. As an epigenetic process that can potentially modify many transcriptional outputs, these mutational events have the potential to change the landscape of the tumour genome through altered expression of global sets of genes and genetic elements. Molecular correlates of patient survival further implicated PI(3)K/AKT as having a role in tumour progression, involving specific DNA methylation events. The PI(3)K/AKT pathway presents a strong therapeutic target in ccRCC, supporting the potential value of MTOR and/or related pathway inhibitor drugs for this cancer^{31, 32}.

Cross-platform molecular analyses indicated a correlation between worsened prognosis in patients with ccRCC and a metabolic shift involving increased dependence on the pentose phosphate shunt, decreased AMPK, decreased Krebs cycle activity, increased glutamine transport and fatty acid production. These findings are consistent with the isotopomer spectral analysis of a pair of *VHL*^{-/-} clear cell kidney cancer cell lines, both of which were notably derived from patients with aggressive, metastatic disease, which revealed a dependence on reductive glutamine metabolism for lipid biosynthesis³³. The metabolic shift identified in poor prognosis ccRCC remarkably mirrors the Warburg metabolic phenotype (increased glycolysis, decreased AMPK, glutamine-dependent lipogenesis) identified in type 2 papillary kidney cancer characterized by mutation of the Krebs cycle enzyme, fumarate hydratase³³. Further studies to dissect out the role of the commonly mutated chromosome 3 chromatin remodelling genes, *PBRM1*, *SETD2* and *BAP1*, in ccRCC tumorigenesis and their potential role in the metabolic remodelling associated with progression of this disease will hopefully provide the foundation for the development of effective forms of therapy for this disease.

Methods

Specimens were obtained from patients, with appropriate consent from institutional review boards. Using a co-isolation protocol, DNA and RNA were purified. In total, 446 patients were assayed on at least one molecular profiling platform, which platforms included: (1) RNA sequencing, (2) DNA methylation arrays, (3) miRNA sequencing, (4) Affymetrix single nucleotide polymorphism (SNP) arrays, (5) exome sequencing, and (6) reverse phase protein arrays. As described above and in the Supplementary Methods, both single platform analyses and integrated cross-platform analyses were performed.

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Author information

Affiliations

Human Genome Sequencing Center, Baylor College of Medicine, Houston, Texas 77030, USA.

Chad J. Creighton, Margaret Morgan, Preethi H. Gunaratne, David A. Wheeler, Richard A. Gibbs, Donna Muzny, Caleb Davis, Liu Xi, Kyle Chang, Nipun Kakkar, Lisa R. Treviño, Susan Benton, Jeffrey G. Reid, Donna Morton, Harsha Doddapaneni, Yi Han, Lora Lewis, Huyen Dinh, Christie Kovar, Yiming Zhu, Jireh Santibanez, Min Wang, Walker Hale & Divya Kalra

Dan L Duncan Cancer Center, Baylor College of Medicine, Houston, Texas 77030, USA.

Chad J. Creighton

Department of Biology & Biochemistry, University of Houston, Houston, Texas 77204, USA.

Preethi H. Gunaratne & Weimin Xiao

Canada's Michael Smith Genome Sciences Centre, BC Cancer Agency, Vancouver, British Columbia V5Z, Canada.

A. Gordon Robertson, Andy Chu, Hye-Jung E. Chun, Andrew J. Mungall, Payal Sipahimalani, Dominik Stoll, Adrian Ally, Miruna Balasundaram, Yaron S. N. Butterfield, Rebecca Carlsen, Candace Carter, Eric Chuah, Robin J. N. Coope, Noreen Dhalla, Sharon Gorski, Ranabir Guin, Carrie Hirst, Martin Hirst, Robert A. Holt, Chandra Lebovitz, Darlene Lee, Haiyan I. Li, Michael Mayo, Richard A. Moore, Erin Pleasance, Patrick Plettner, Jacqueline E. Schein, Arash Shafiei, Jared R. Slobodan, Angela Tam, Nina Thiessen, Richard J. Varhol, Natasja Wye, Yongjun Zhao, Inanc Birol, Steven J. M. Jones & Marco A. Marra

Department of Medicine, Harvard Medical School, Boston, Massachusetts 02215, USA.

Rameen Beroukhim

The Eli and Edythe L. Broad Institute of Massachusetts Institute of Technology and Harvard University, Cambridge, Massachusetts 02142, USA.

Rameen Beroukhim, Kristian Cibulskis, Gad Getz, Michael S. Lawrence, Carrie Sougnez, Scott L. Carter, Andrey Sivachenko, Lee Lichtenstein, Chip Stewart, Doug Voet, Sheila Fisher, Stacey B. Gabriel, Eric Lander, Steve E. Schumacher, Barbara Tabak, Gordon Saksena, Robert C. Onofrio, Andrew D. Cherniack, Jeff Gentry, Kristin Ardlie, Carrie Sougnez, Stacey B. Gabriel, Matthew Meyerson, Michael S. Noble, Daniel DiCara, Hailei Zhang, Juok Cho, David I. Heiman, Nils Gehlenborg, William Mallard, Pei Lin, Scott Frazer, Petar Stojanov, Yingchun Liu, Lihua Zhou, Jaegil Kim & Lynda Chin

Department of Pathology, Harvard Medical School, Boston, Massachusetts 02215, USA.

Sabina Signoretti & Matthew Meyerson

Department of Computer Science, Brown University, Providence, Rhode Island 02912, USA.

Fabio Vandin Hsin-Ta Wu, Benjamin J. Raphael, Fabio Vandin & Hsin-Ta Wu

Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030, USA.

Roel G. W. Verhaak, Wandaliz Torres-Garcia, Rehan Akbani, John N. Weinstein, Roel G.W. Verhaak, Rahul Vegesna, Hoon Kim, Eric Jonasch, Zhiyong Ding, Nianxiang Zhang, Anna K. Unruh, Tod D. Casasent & Chris Wakefield

Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030, USA.

Pheroze Tamboli, Wei Zhang, David Cogdell, Bogdan A. Czerniak & Kenneth D. Aldape

Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, New York 10065, USA.

Victor Reuter, A. Rose Brannon, Michael F. Berger & Satish Tickoo

Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, New York, New York 10065, USA.

James J. Hsieh, A. Ari Hakimi & Marc Ladanyi

Computational Biology Center, Memorial Sloan-Kettering Cancer Center, New York, New York 10065, USA.

Anders Jacobsen, Giovanni Ciriello, Boris Reva, Nikolaus Schultz, Yevgeniy Antipin, Jianjiong Gao, Ethan Cerami, Benjamin Gross, B. Arman Aksoy, Rileen Sinha, Nils Weinhold, S. Onur Sumer, Barry S. Taylor, Ronglai Shen & Chris Sander

Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland 20892, USA.

Christopher J. Ricketts, W. Marston Linehan, Cathy D. Vocke, James Peterson, Robert Worrell, Maria J. Merino & Laura S. Schmidt

Department of Biomolecular Engineering and Center for Biomolecular Science and Engineering, University of California Santa Cruz, Santa Cruz, California 95064, USA.

Joshua M. Stuart, Sam Ng, Evan O. Paull, Daniel Carlin, Theodore Goldstein, Peter Waltman, Kyle Ellrott, Jing Zhu & David Haussler

Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, USA.

W. Kimryn Rathmell, Katherine A. Hoadley, Christina Liquori, Yidi J. Turman, Yan Shi, Scot Waring, Elizabeth Buda, Jesse Walsh, Junyuan Wu, Tom Bodenheimer, Alan P. Hoyle, Janae V. Simons, Mathew G. Soloway, Saianand Balu, Joel S. Parker, D. Neil Hayes, Charles M. Perou, Leigh Thorne, Lori Boice, Mei Huang & Jennifer C. Fisher

USC Epigenome Center, University of Southern California, Los Angeles, California 90033, USA.

Hui Shen, Peter W. Laird, Timothy Triche Jr, Daniel J. Weisenberger, Phillip H. Lai, Moiz S. Bootwalla, Dennis T. Maglinte, Swapna Mahurkar, Benjamin P. Berman & David J. Van Den Berg

Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, USA.

J.Todd Auman

Carolina Center for Genome Sciences, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, USA.

Donghui Tan

Department of Biology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, USA.

Corbin D. Jones

Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill, Chapel Hill, Chapel Hill, North Carolina 27599, USA.

Katherine A. Hoadley, Lisle E. Mose, Michael D. Topal & Charles M. Perou

Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, USA.

Katherine A. Hoadley, Piotr A. Mieczkowski, Stuart R. Jefferys, Michael D. Topal & Charles M. Perou

Department of Internal Medicine, Division of Medical Oncology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, USA.

D. Neil Hayes

Department of Genetics, Harvard Medical School, Boston, Massachusetts 02215, USA.

Raju Kucherlapati

Division of Genetics, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA.

Raju Kucherlapati & Peter Park

The Center for Biomedical Informatics, Harvard Medical School, Boston, Massachusetts 02115, USA.

Peter Park & Nils Gehlenborg

Informatics Program, Children's Hospital, Boston, Massachusetts 02115, USA.

Peter Park

Cancer Biology Division, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, Maryland 21231, USA.

Leslie Cope & Stephen B. Baylin

Institute for Systems Biology, Seattle, Washington 98109, USA.

Sheila M. Reynolds & Ilya Shmulevich

Department of Systems Biology, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030, USA.

Yiling Lu, Dimitra Tsavachidou & Gordon B. Mills

Department of Genomic Medicine, University of Texas MD Anderson Cancer Center, Houston, Texas 77054, USA.

Lynda Chin

Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York 10065, USA.

Irina Ostrovnaya

Department of Molecular & Medical Genetics, Oregon Health & Science University, Portland, Oregon 97239, USA.

Suzanne S. Fei, Andrew Stout & Paul T. Spellman

Department of Radiology, Stanford University Medical Center, Stanford, California 94305, USA.

Daniel L. Rubin & Tiffany T. Liu

Howard Hughes Medical Institute, University of California Santa Cruz, Santa Cruz, California 95064, USA.

David Haussler

International Genomics Consortium, Phoenix, Arizona 85004, USA.

Candace Shelton, Johanna Gardner, Robert Penny, Mark Sherman, David Mallery, Scott Morris, Joseph Paulauskis, Ken Burnett, Troy Shelton & Erin Curley

Georgetown-Lombardi Comprehensive Cancer Center, Georgetown University, Washington DC 20057, USA.

Michael B. Atkins

Basic Science Program, SAIC-Frederick, Inc., Frederick National Lab, Frederick, Maryland 21702, USA.

Laura S. Schmidt

Department of Urology, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030, USA.

Christopher G. Wood

Cancer Biology Program, Fox Chase Cancer Center, Philadelphia, Pennsylvania 19111, USA.

Jeff Boyd & JoEllen Weaver

Helen F. Graham Cancer Center, Christiana Care, Newark, Delaware 19713, USA.

Mary V. Iacocca, Nicholas Petrelli, Gary Witkin, Jennifer Brown, Christine Czerwinski, Lori Huelsenbeck-Dill & Brenda Rabeno

Penrose-St. Francis Health Services, Colorado Springs, Colorado 80907, USA.

Jerome Myers, Carl Morrison, Julie Bergsten, John Eckman, Jodi Harr, Christine Smith, Kelinda Tucker & Leigh Anne Zach

Department of Pathology, Roswell Park Cancer Institute, Buffalo, New York 14263, USA.

Wiam Bshara, Carmelo Gaudio & Carl Morrison

Department of Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania 15213, USA.

Rajiv Dhir, Jodi Maranchie, Joel Nelson & Anil Parwani

Cureline, Inc. South San Francisco, California 94080, USA.

Olga Potapova

St Petersburg City Clinical Oncology Dispensary, St Petersburg 198255, Russia.

Konstantin Fedosenko

Department of Pathology and Laboratory Medicine, Weill Cornell College of Medicine, New York, New York 10065, USA.

Juan M. Mosquera & Mark A. Rubin

Department of Urology, Massachusetts General Hospital, Boston, Massachusetts 02114, USA.

Michael L. Blute

SRA International, 4300 Fair Lakes Court, Fairfax, Virginia 22033, USA.

Todd Pihl, Mark Jensen, Robert Sfeir, Ari Kahn, Anna Chu, Prachi Kothiyal, Eric Snyder, Joan Pontius, Brenda Ayala, Mark Backus, Jessica Walton, Julien Baboud, Dominique Berton, Matthew Nicholls, Deepak Srinivasan, Rohini Raman, Stanley Girshik, Peter Kigonya, Shelley Alonso, Rashmi Sanbhadti, Sean Barletta & David Pot

The Cancer Genome Atlas Program Office, Center for Cancer Genomics, National Cancer Institute, Bethesda, Maryland 20892, USA.

Margi Sheth, John A. Demchok, Tanja Davidsen, Zhining Wang, Liming Yang, Roy W. Tarnuzzer, Jiashan Zhang & Kenna R. Mills Shaw

TCGA Consultant, Scimentis, LLC, Atlanta, Georgia 30666, USA.

Greg Eley

MLF Consulting, Arlington, Massachusetts 02474, USA.

Martin L. Ferguson

National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.

Mark S. Guyer, Bradley A. Ozenberger & Heidi J. Sofia.

Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts 02215, USA.

Sabina Signoretti, Rameen Beroukhim, Matthew Meyerson, Petar Stojanov, William G. Kaelin & Toni Choueiri

Buck Institute for Research on Aging, Novato, California 94945, USA.

Christopher Benz & Christina Yau

Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, Massachusetts 02215, USA.

Rameen Beroukhim, Steve E. Schumacher & Barbara Tabak

Cancer Center and Department of Pathology, Massachusetts General Hospital, 55 Fruit St, Boston, Massachusetts 02114.

Gad Getz

Mayo Clinic, Rochester, Minnesota 55905, USA.

John C. Cheville & R. Houston Thompson

Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts 02215, USA.

Sabina Signoretti

Howard Hughes Medical Institute, Chevy Chase, Maryland 20815, USA.

William G. Kaelin

Consortia

The Cancer Genome Atlas Research Network

Analysis working group: Baylor College of Medicine

Chad J. Creighton, Margaret Morgan, Preethi H. Gunaratne, David A. Wheeler & Richard A. Gibbs

BC Cancer Agency

A. Gordon Robertson & Andy Chu

Broad Institute

Rameen Beroukhim & Kristian Cibulskis

Brigham & Women's Hospital

Sabina Signoretti

Brown University

Fabio Vandin Hsin-Ta Wu & Benjamin J. Raphael

The University of Texas MD Anderson Cancer Center

Roel G. W. Verhaak, Pheroze Tamboli, Wandaliz Torres-Garcia, Rehan Akbani & John N. Weinstein

Memorial Sloan-Kettering Cancer Center

Victor Reuter, James J. Hsieh, A. Rose Brannon, A. Ari Hakimi, Anders Jacobsen, Giovanni Ciriello & Boris Reva

National Cancer Institute

Christopher J. Ricketts & W. Marston Linehan

University of California Santa Cruz

Joshua M. Stuart

University of North Carolina, Chapel Hill

W. Kimryn Rathmell

University of Southern California

Hui Shen & Peter W. Laird

Genome sequencing centres: Baylor College of Medicine

Donna Muzny, Caleb Davis, Margaret Morgan, Liu Xi, Kyle Chang, Nipun Kakkar, Lisa R. Treviño, Susan Benton, Jeffrey G. Reid, Donna Morton, Harsha Doddapaneni, Yi Han, Lora Lewis, Huyen Dinh, Christie Kovar, Yiming Zhu, Jireh Santibanez, Min Wang, Walker Hale, Divya Kalra, Chad J. Creighton, David A. Wheeler & Richard A. Gibbs

Broad Institute

Gad Getz, Kristian Cibulskis, Michael S. Lawrence, Carrie Sougnez, Scott L. Carter, Andrey Sivachenko, Lee Lichtenstein, Chip Stewart, Doug Voet, Sheila Fisher, Stacey B. Gabriel & Eric Lander

Genome characterization centres: Broad Institute

Rameen Beroukhi, Steve E. Schumacher, Barbara Tabak, Gordon Saksena, Robert C. Onofrio, Scott L. Carter, Andrew D. Cherniack, Jeff Gentry, Kristin Ardlie, Carrie Sougnez, Gad Getz, Stacey B. Gabriel & Matthew Meyerson

BC Cancer Agency

A. Gordon Robertson, Andy Chu, Hye-Jung E. Chun, Andrew J. Mungall, Payal Sipahimalani, Dominik Stoll, Adrian Ally, Miruna Balasundaram, Yaron S. N. Butterfield, Rebecca Carlsen, Candace Carter, Eric Chuah, Robin J. N. Coope, Noreen Dhalla, Sharon Gorski, Ranabir Guin, Carrie Hirst, Martin Hirst, Robert A. Holt, Chandra Lebovitz, Darlene Lee, Haiyan I. Li, Michael Mayo, Richard A. Moore, Erin Pleasance, Patrick Plettner, Jacqueline E. Schein, Arash Shafiei, Jared R. Slobodan, Angela Tam, Nina Thiessen, Richard J. Varhol, Natasja Wye, Yongjun Zhao, Inanc Birol, Steven J. M. Jones & Marco A. Marra

University of North Carolina, Chapel Hill

J.Todd Auman, Donghui Tan, Corbin D. Jones, Katherine A. Hoadley, Piotr A. Mieczkowski, Lisle E. Mose, Stuart R. Jefferys, Michael D. Topal, Christina Liquori, Yidi J. Turman, Yan Shi, Scot Waring, Elizabeth Buda, Jesse Walsh, Junyuan Wu, Tom Bodenheimer, Alan P. Hoyle, Janae V. Simons, Mathew G. Soloway, Saianand Balu, Joel S. Parker, D. Neil Hayes & Charles M. Perou

Harvard Medical School

Raju Kucherlapati & Peter Park

University of Southern California & Johns Hopkins University

Hui Shen, Timothy Triche Jr, Daniel J. Weisenberger, Phillip H. Lai, Moiz S. Bootwalla, Dennis T. Maglinte, Swapna Mahurkar, Benjamin P. Berman, David J. Van Den Berg, Leslie Cope, Stephen B. Baylin & Peter W. Laird

Genome data analysis: Baylor College of Medicine

Chad J. Creighton & David A. Wheeler

Broad Institute

Gad Getz, Michael S. Noble, Daniel DiCara, Hailei Zhang, Juok Cho, David I. Heiman, Nils Gehlenborg, Doug Voet, William Mallard, Pei Lin, Scott Frazer, Petar Stojanov, Yingchun Liu, Lihua Zhou, Jaegil Kim, Michael S. Lawrence & Lynda Chin

Brown University

Fabio Vandin, Hsin-Ta Wu & Benjamin J. Raphael

Buck Institute for Research on Aging

Christopher Benz & Christina Yau

Institute for Systems Biology

Sheila M. Reynolds & Ilya Shmulevich

The University of Texas MD Anderson Cancer Center

Roel G.W. Verhaak, Wandaliz Torres-Garcia, Rahul Vegesna, Hoon Kim, Wei Zhang, David Cogdell, Eric Jonasch, Zhiyong Ding, Yiling Lu, Rehan Akbani, Nianxiang Zhang, Anna K. Unruh, Tod D. Casasent, Chris Wakefield, Dimitra Tsavachidou, Lynda Chin, Gordon B. Mills & John N. Weinstein

Memorial Sloan-Kettering Cancer Center

Anders Jacobsen, A. Rose Brannon, Giovanni Ciriello, Nikolaus Schultz, A. Ari Hakimi, Boris Reva, Yevgeniy Antipin, Jianjiong Gao, Ethan Cerami, Benjamin Gross, B. Arman Aksoy, Rileen Sinha, Nils Weinhold, S. Onur Sumer, Barry S. Taylor, Ronglai Shen, Irina Ostrovskaya, James J. Hsieh, Michael F. Berger, Marc Ladanyi & Chris Sander

Oregon Health & Science University

Suzanne S. Fei, Andrew Stout & Paul T. Spellman

Stanford University

Daniel L. Rubin & Tiffany T. Liu

University of California Santa Cruz

Joshua M. Stuart, Sam Ng, Evan O. Paull, Daniel Carlin, Theodore Goldstein, Peter Waltman, Kyle Ellrott, Jing Zhu & David Haussler

University of Houston

Preethi H. Gunaratne & Weimin Xiao

Biospecimen core resource: International Genomics Consortium

Candace Shelton, Johanna Gardner, Robert Penny, Mark Sherman, David Mallery, Scott Morris, Joseph Paulauskis, Ken Burnett & Troy Shelton

Tissue source sites: Brigham & Women's Hospital

Sabina Signoretti &

Dana-Farber Cancer Institute

William G. Kaelin & Toni Choueiri

Georgetown University

Michael B. Atkins

International Genomics Consortium

Robert Penny, Ken Burnett, David Mallery & Erin Curley

Memorial Sloan-Kettering Cancer Center

Satish Tickoo & Victor Reuter

University of North Carolina at Chapel Hill

W. Kimryn Rathmell, Leigh Thorne, Lori Boice, Mei Huang & Jennifer C. Fisher

National Cancer Institute

W. Marston Linehan, Cathy D. Vocke, James Peterson, Robert Worrell, Maria J. Merino & Laura S. Schmidt

The University of Texas MD Anderson Cancer Center

Pheroze Tamboli, Bogdan A. Czerniak, Kenneth D. Aldape & Christopher G. Wood

Fox Chase Cancer Center

Jeff Boyd & JoEllen Weaver

Helen F Graham Cancer Center at Christiana Care

Mary V. Iacocca, Nicholas Petrelli, Gary Witkin, Jennifer Brown, Christine Czerwinski, Lori Huelsenbeck-Dill & Brenda Rabeno

Penrose-St. Francis Health Services

Jerome Myers, Carl Morrison, Julie Bergsten, John Eckman, Jodi Harr, Christine Smith, Kelinda Tucker & Leigh Anne Zach

Roswell Park Cancer Institute

Wiam Bshara, Carmelo Gaudioso & Carl Morrison

University of Pittsburgh

Rajiv Dhir, Jodi Maranchie, Joel Nelson & Anil Parwani

Cureline

Olga Potapova

St. Petersburg City Clinical Oncology Dispensary

Konstantin Fedosenko

Mayo Clinic

John C. Cheville & R. Houston Thompson

Disease working group: Brigham & Women's Hospital

Sabina Signoretti

Dana-Farber Cancer Institute

William G. Kaelin

Georgetown University

Michael B. Atkins

Memorial Sloan-Kettering Cancer Center

Satish Tickoo & Victor Reuter

National Cancer Institute

W. Marston Linehan, Cathy D. Vocke, James Peterson, Maria J. Merino & Laura S. Schmidt

The University of Texas MD Anderson Cancer Center

Pheroze Tamboli

Weill Cornell Medical College

Juan M. Mosquera & Mark A. Rubin

Massachusetts General Hospital

Michael L. Blute

University of North Carolina, Chapel Hill

W. Kimryn Rathmell

Data coordination centre

Todd Pihl, Mark Jensen, Robert Sfeir, Ari Kahn, Anna Chu, Prachi Kothiyal, Eric Snyder, Joan Pontius, Brenda Ayala, Mark Backus, Jessica Walton, Julien Baboud, Dominique Berton, Matthew Nicholls, Deepak Srinivasan, Rohini Raman, Stanley Girshik, Peter Kigonya, Shelley Alonso, Rashmi Sanbhadti, Sean Barletta & David Pot

Project team: National Cancer Institute

Margi Sheth, John A. Demchok, Tanja Davidsen, Zhining Wang, Liming Yang, Roy W. Tarnuzzer, Jiashan Zhang, Greg Eley, Martin L. Ferguson & Kenna R. Mills Shaw

National Human Genome Research Institute

Mark S. Guyer, Bradley A. Ozenberger & Heidi J. Sofia.

Contributions

The Cancer Genome Atlas research network contributed collectively to this study. Biospecimens were provided by the tissue source sites and processed by the Biospecimen Core Resource. Data generation and analyses were performed by the genome-sequencing centers, cancer genome-characterization centers and genome data analysis centers. All data were released through the Data Coordinating Center. Project activities were coordinated by the NCI and NHGRI project teams. The following TCGA investigators of the Kidney Analysis Working Group contributed substantially to the analysis and writing of this manuscript: Project leaders: Richard A. Gibbs, W. Marston Linehan. Data Coordinator: Margaret Morgan. Analysis Coordinators: Chad J. Creighton, Roel G. W. Verhaak. Manuscript Coordinators: Richard A. Gibbs, Chad J. Creighton. Writing Team: W. Marston Linehan, Chad J. Creighton, W. Kimryn Rathmell, Roel G. W. Verhaak, Richard A. Gibbs. DNA Sequence analysis: David A Wheeler, Kristian Cibulskis. mRNA analysis: Roel G. W. Verhaak, A. Rose Brannon, W. Kimryn Rathmell, Wandaliz Torres-Garcia. microRNA analysis: A. Gordon Robertson, Andy Chu, Preethi H. Gunaratne. DNA methylation analysis: Hui Shen, Peter W. Laird. Copy number analysis: Rameen Beroukhim, Sabina Signoretti. Protein analysis: Dimitra Tsavachidou, Yiling Lu, Gordon B Mills. Pathway/Integrated Analysis: Rehan Akbani, Giovanni Ciriello, Chad J. Creighton, Suzanne S. Fei, Anders Jacobsen, Evan O. Paull, Ben Raphael, Sheila M. Reynolds, Christopher J. Ricketts, Nikolaus Schultz, Joshua M. Stuart, Fabio Vandin. Clinical Data: W. Kimryn Rathmell, A. Ari Hakimi, Johanna Gardener, Candace Shelton. Pathology and Clinical Expertise: James Hsieh, Marston W. Linehan, Pheroze Tamboli, W. Kimryn Rathmell, Victor Reuter.

Competing financial interests

The authors declare no competing financial interests.

Corresponding author

Correspondence to: W. Marston Linehan

All of the primary sequence files are deposited inCGHub (file IDs in Supplementary Information) and all other data are deposited at the Data Coordinating Centrer (DCC) for public access (<http://cancergenome.nih.gov/>).

Supplementary information**PDF files**

1. Supplementary Information (10.3 MB)

This file contains Supplementary Text and Data, Supplementary Figures 1-62, Supplementary Tables 1-24 - see contents for details.

Zip files

1. Supplementary Data (8.1 MB)

This zipped file contains Supplementary Data sets 1-10: Data File S1 contains sample list for Core and Extended sets; Data File S2 contains clinical dataset used in the study; Data File S3 contains significantly mutated genes; Data File S4 contains mRNA fusion results; Data File S5 contains mRNA subtype analysis results; Data File S6 contains analysis of known oncogenes and tumor suppressors in ccRCC; Data File S7 contains pathmark pathway enrichment results; Data File S8 contains Molecular prognostic signatures; Data File S9 contains mRNA and miRNA-based subtyping assignments by sample and Data File S10 contains complete Mutation Annotation File (MAF) for exome sequencing.



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