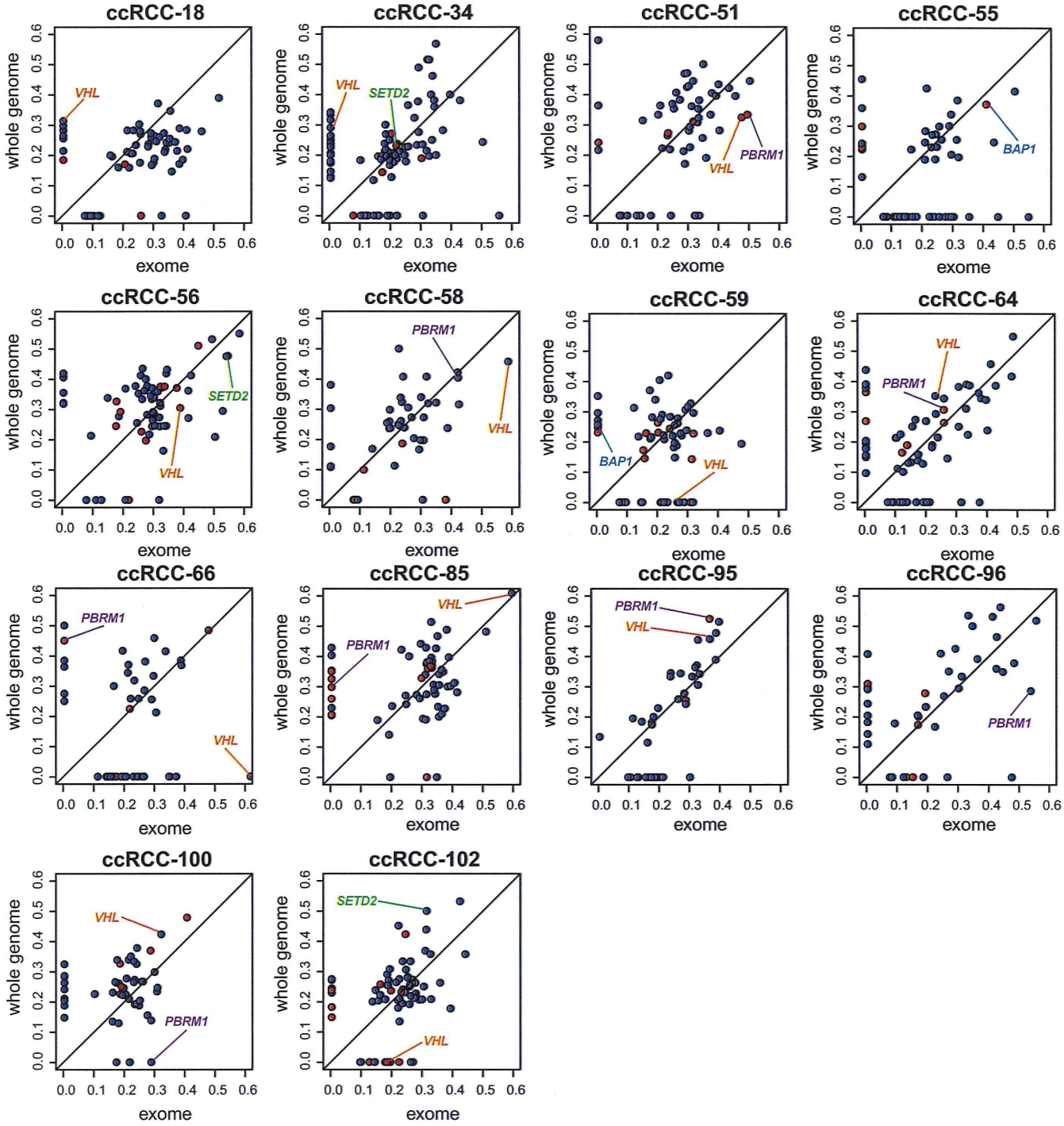
Supplementary Figure 5



Diagonal plots of validated coding sequence mutations detected by whole-genome and/or exome sequencing for 14 ccRCC specimens analyzed with both platforms

Observed allele frequencies from both sequencing platforms are plotted for each mutation. Major driver mutations are indicated. SNVs are shown in blue whereas indels are shown in red.

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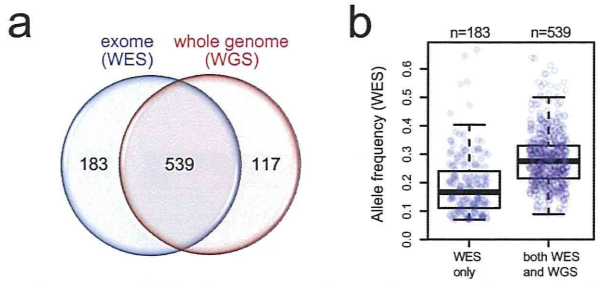
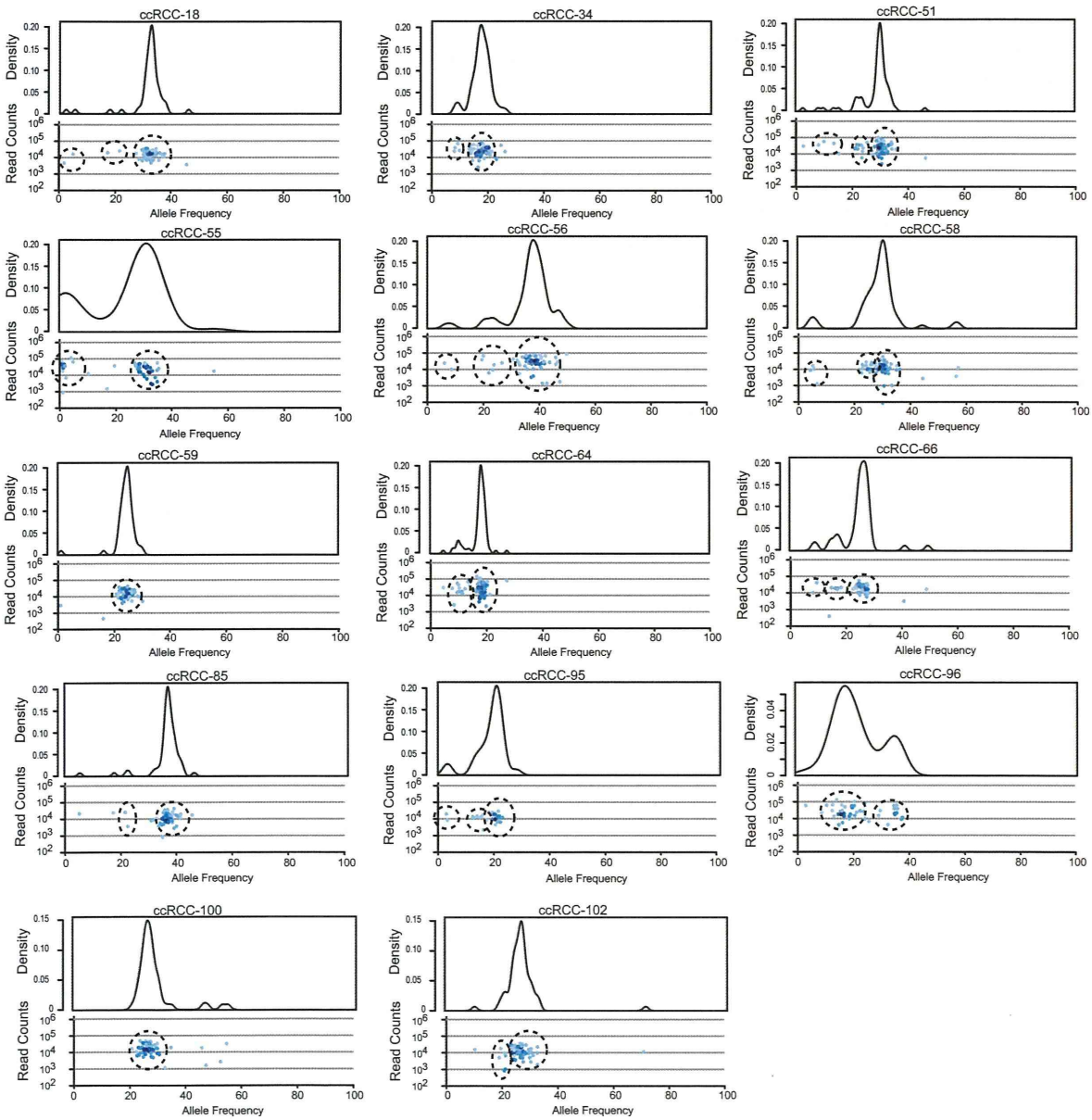
Supplementary Figure 6



Lower allele frequencies of somatic mutations detected only by whole-exome sequencing for 14 ccRCC specimens

(**a**) Number of confirmed somatic mutations detected by whole-genome and/or exome sequencing. (**b**) Comparisons of allele frequencies between validated somatic mutations detected by whole-exome sequencing only and by both whole-genome and exome sequencing.

Supplementary Figure 7

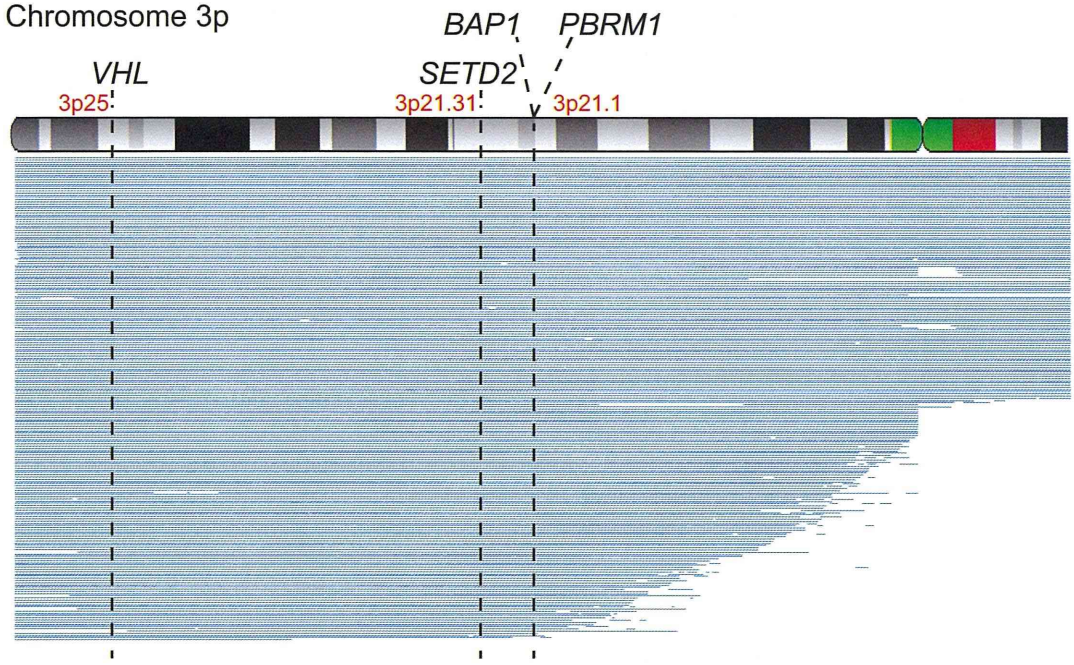


Intratumoral heterogeneity in ccRCC cases

Kernel density estimations of clonal populations based on allele frequencies of observed somatic mutations using deep sequencing (top panels).The frequency of each variant allele is plotted against the total number of sequencing reads that covered the corresponding nucleotide positions (bottom panels).

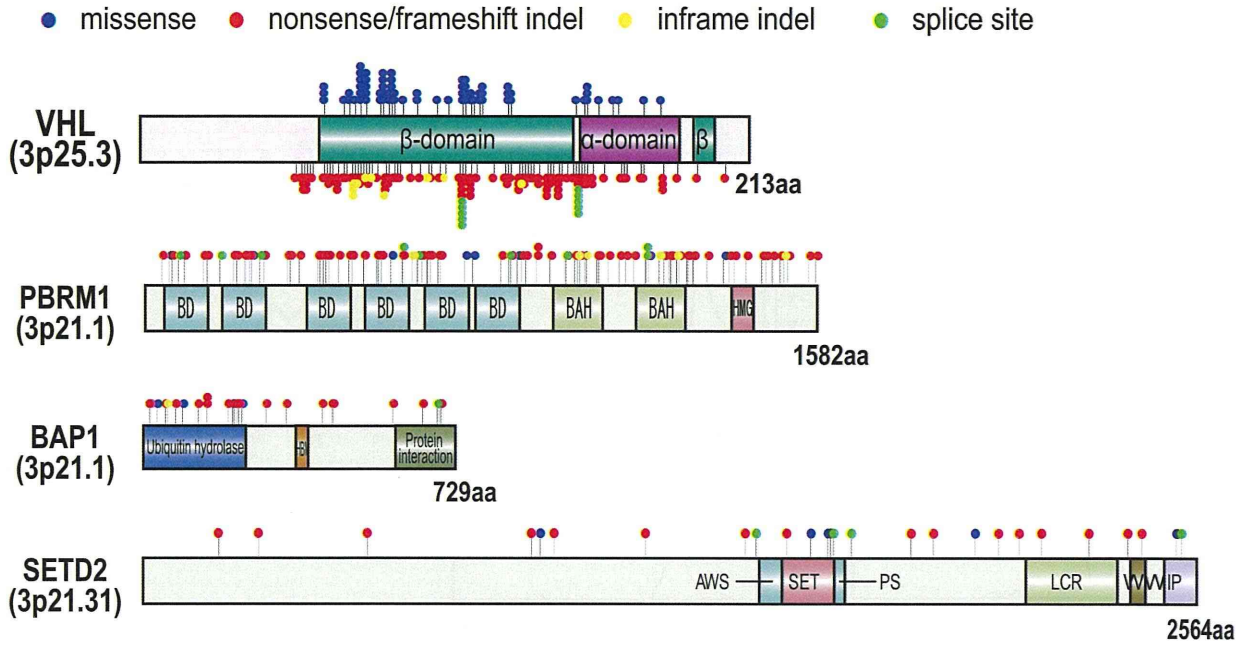
Nature Genetics: doi:10.1038/ng.2699

Supplementary Figure 8



LOH mapping in the 3p arm in ccRCC
LOH in the 3p arm found in a total of 226 ccRCC cases by SNP array analysis. The genetic loci of the 4 major targets of 3p LOH are indicated in which the *PBRM1* locus demarcates the common LOH regions.

Supplementary Figure 9



Mutation distributions in 3p targets, including *VHL*, *PBRM1*, *SETD2* and *BAP1*
Mutations of *VHL, PBRM1, SETD2* and *BAP1* in a cohort of 240 ccRCC cases. Types of mutations are distinguished by the indicated colors.

Nature Genetics: doi:10.1038/ng.2699

Supplementary Figure 10

Elongin C (*TCEB1*)

```
[Homo sapiens]                  NP_001191786.1   1 ------------MDGEEKTYGGCEGPDAMYVKLISSDGHEFIVKREHALT  38
[Pan troglodytes]               XP_001154170.1   1 ------------MDGEEKTYGGCEGPDAMYVKLISSDGHEFIVKREHALT  38
[Pan troglodytes]               XP_003311809.1   1 ------------MDGEEKTYGGCEGPDAMYVKLISSDGHEFIVKREHALT  38
[Macaca mulatta]                XP_002805434.1   1 ------------MDGEEKTYGGCEGPDAMYVKLISSDGHEFIVKREHALT  38
[Canis lupus familiaris]        XP_535104.1      1 ------------MDGEEKTYGGCEGPDAMYVKLISSDGHEFIVKREHALT  38
[Bos taurus]                    NP_001039958.1   1 ------------MDGEEKTYGGCEGPDAMYVKLISSDGHEFIVKREHALT  38
[Mus musculus]                  NP_080732.1      1 ------------MDGEEKTYGGCEGPDAMYVKLISSDGHEFIVKREHALT  38
[Rattus norvegicus]             NP_072115.1      1 ------------MDGEEKTYGGCEGPDAMYVKLISSDGHEFIVKREHALT  38
[Gallus gallus]                 NP_001007889.1   1 ------------MDGEEKTYGGCEGPDAMYVKLISSDGHEFIVKREHALT  38
[Danio rerio]                   NP_001002440.2   1 ------------MDSEEKTYGGCEGPDAMYVKLISSDGHEFIVKREHALT  38
[Drosophila melanogaster]       NP_725894.1      1 -------MIAMDEQRGDKIYGGCEGPDAMYVKLISSDGHEFVVKREHALT  43
[Anopheles gambiae str. PEST]   XP_309973.2      1 -------NNMEERTGTERIYGGCEGPDAMYVKLISSDGHEFIVKREHALT  43
[Caenorhabditis elegans]        NP_497405.1      1 MADQNNAIQCDQDAAQPKQYGGIEGPTSQYVKLVSSDDHEFIIKRELALT  50

                                              Y79S
                                              Y79C                 A100P
                                               ▼                     ▼
39 SGTIKAMLSGPGQFAENETNEVNFREIPSHVLSKVCMYFTYKVRYTNSSTEIPEFPIAPEIALELLMAANFLDC  112
39 SGTIKAMLSGPGQFAENETNEVNFREIPSHVLSKVCMYFTYKVRYTNSSTEIPEFPIAPEIALELLMAANFLDC  112
39 SGTIKAMLSGPGQFAENETNEVNFREIPSHVLSKVCMYFTYKVRYTNSSTEIPEFPIAPEIALELLMAANFLDC  112
39 SGTIKAMLSGPGQFAENETNEVNFREIPSHVLSKVCMYFTYKVRYTNSSTEIPEFPIAPEIALELLMAANFLDC  112
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39 SGTIKAMLSGPGQFAENETNEVNFREIPSHVLSKVCMYFTYKVRYTNSSTEIPEFPIAPEIALELLMAANFLDC  112
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39 SGTIKAMLSGPGQFAENETNEVNFREIPSHVLSKVCMYFTYKVRYTNSSTEIPEFPIAPEIALELLMAANFLDC  112
39 SGTIKAMLSGPGQFAENETNEVNFREIPSHVLSKVCMYFTYKVRYTNSSTEIPEFPIAPEIALELLMAANFLDC  112
44 SGTIRAMLSGPGQFAENEANEVHFREIPSHVLQKVCMYFTYKVRYTNSSTEIPEFPIAPEIALELLMAANFLDC  117
44 SGTIKAMLSGPGQFAENEANEVNFREIPSHVLEKVCMYFTYKVRYTNSSTEIPEFPIAPEIALELLMAANFLDC  117
51 SGTIRAMLSGPGVYAENESNVVYFREIPSHVLQKVCQYFAYKVRYTHAATEIPEFPIPPDVALELLMAANFLDC  124
```
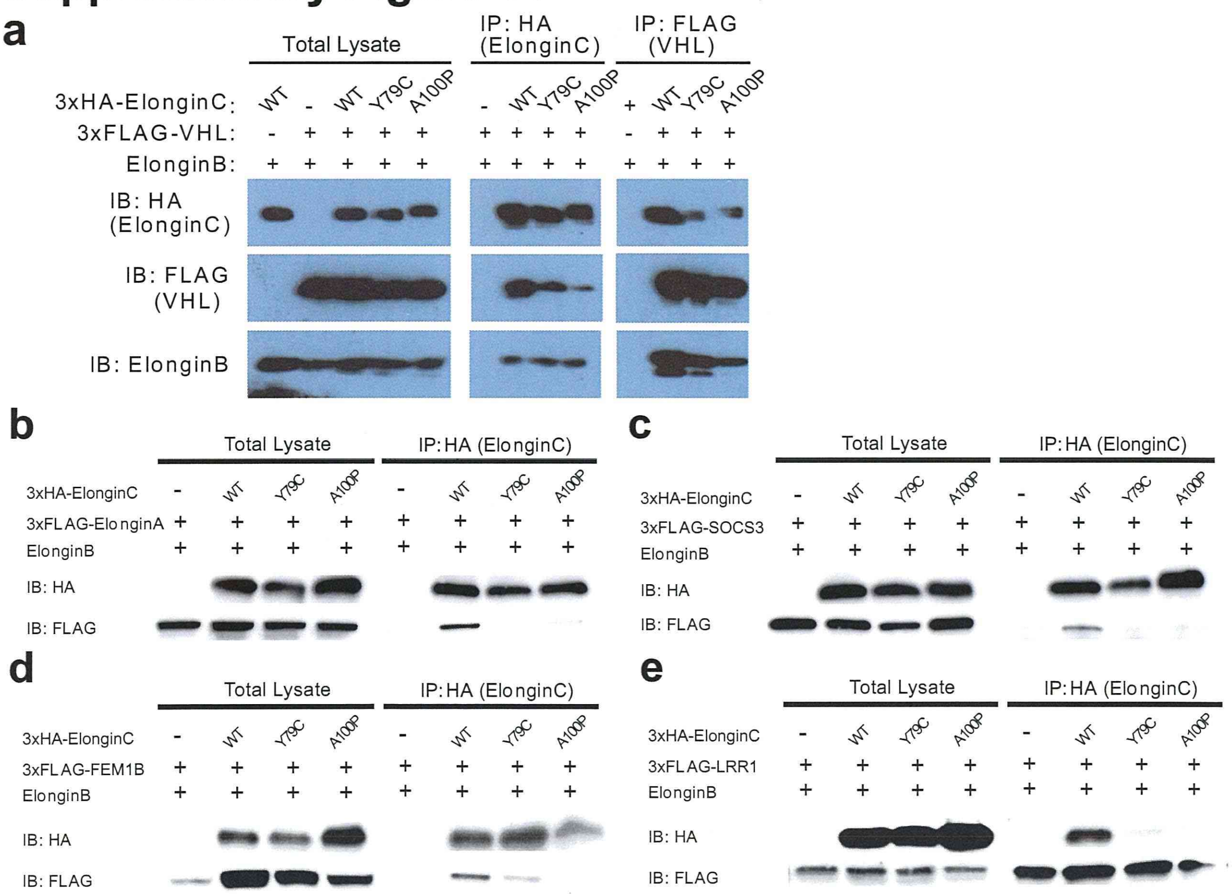

Amino-acid sequence alignments for Elongin C (TCEB1) from different species
Completely conserved amino acids among all species are indicated in blue; mutational hot spots are shown in red.

Supplementary Figure 11



Compromised binding of mutant Elongin C (TCEB1) to VHL and other BC-box proteins
(**a**) Western blotting for indicated components of the VHL complex in total cell lysates (left panels), and precipitated with anti-HA (Elongin C) (middle panels) and anti-FLAG (VHL) in lysates from 293T cells transduced with the indicated mock, wild-type or mutant 3xHA-tagged Elongin C, Elongin B and 3xFLAG-tagged VHL. (**b-e**) Western blot analyses of BC-box proteins in total cell lysates (left panels) and precipitated with anti-HA (Elongin C) or anti-FLAG (BC-box protein) (right panels) in lysates from 293T cells transduced with either mock, wild-type, mutant 3xHAtagged Elongin C, Elongin B and 3xFLAG-tagged Elongin A (**b**), SOCS3 (**c**), FEM1B (**d**) and LRR1 (**e**).

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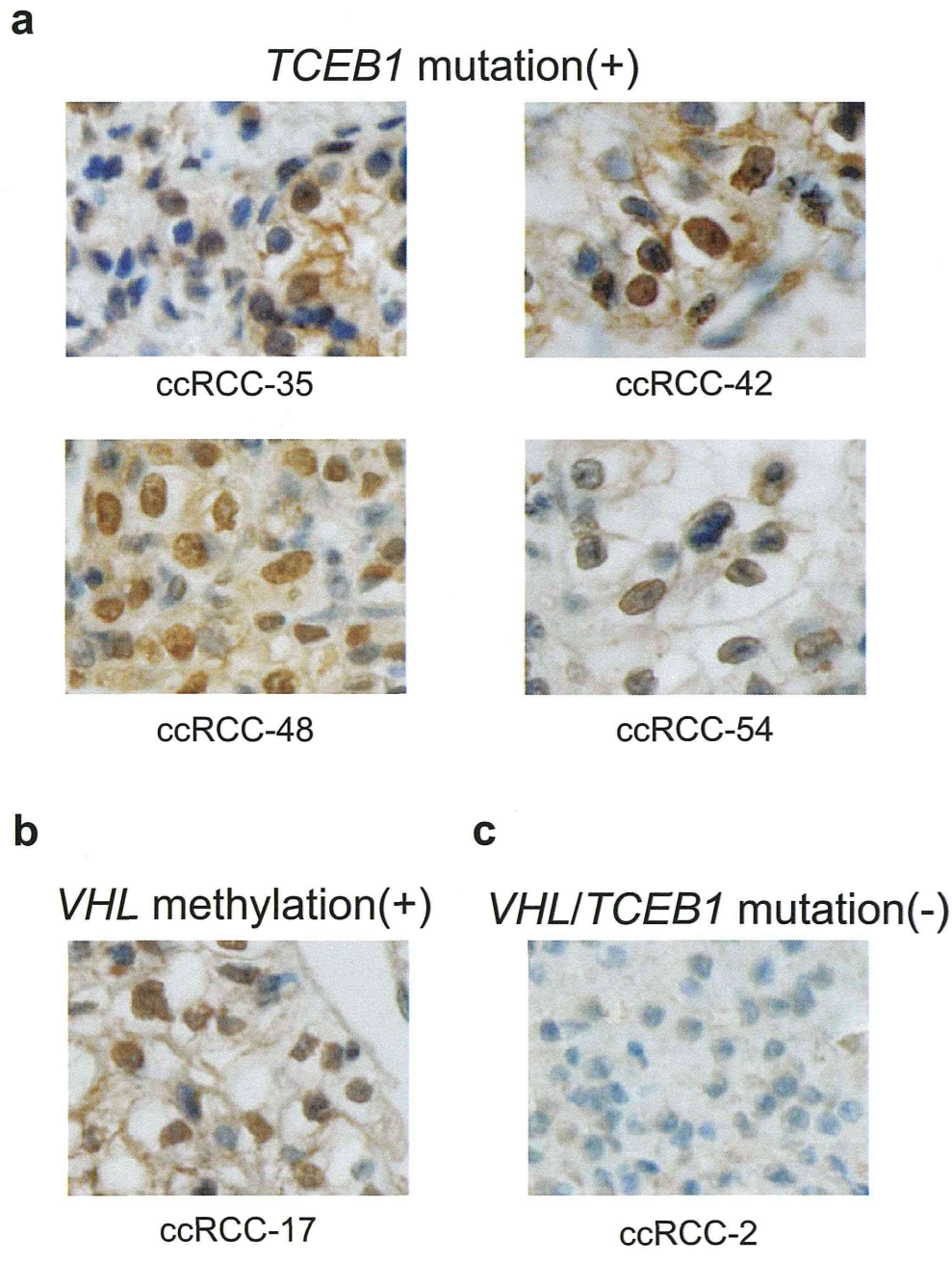
Supplementary Figure 12



HIF1α expression in IHC
Increased HIF expression was confirmed in *TCEB1* mutated tumors (**a**) as well as a tumor with *VHL* promoter methylation (**b**), but not in a tumor without *VHL*/*TCEB1* alterations (**c**).

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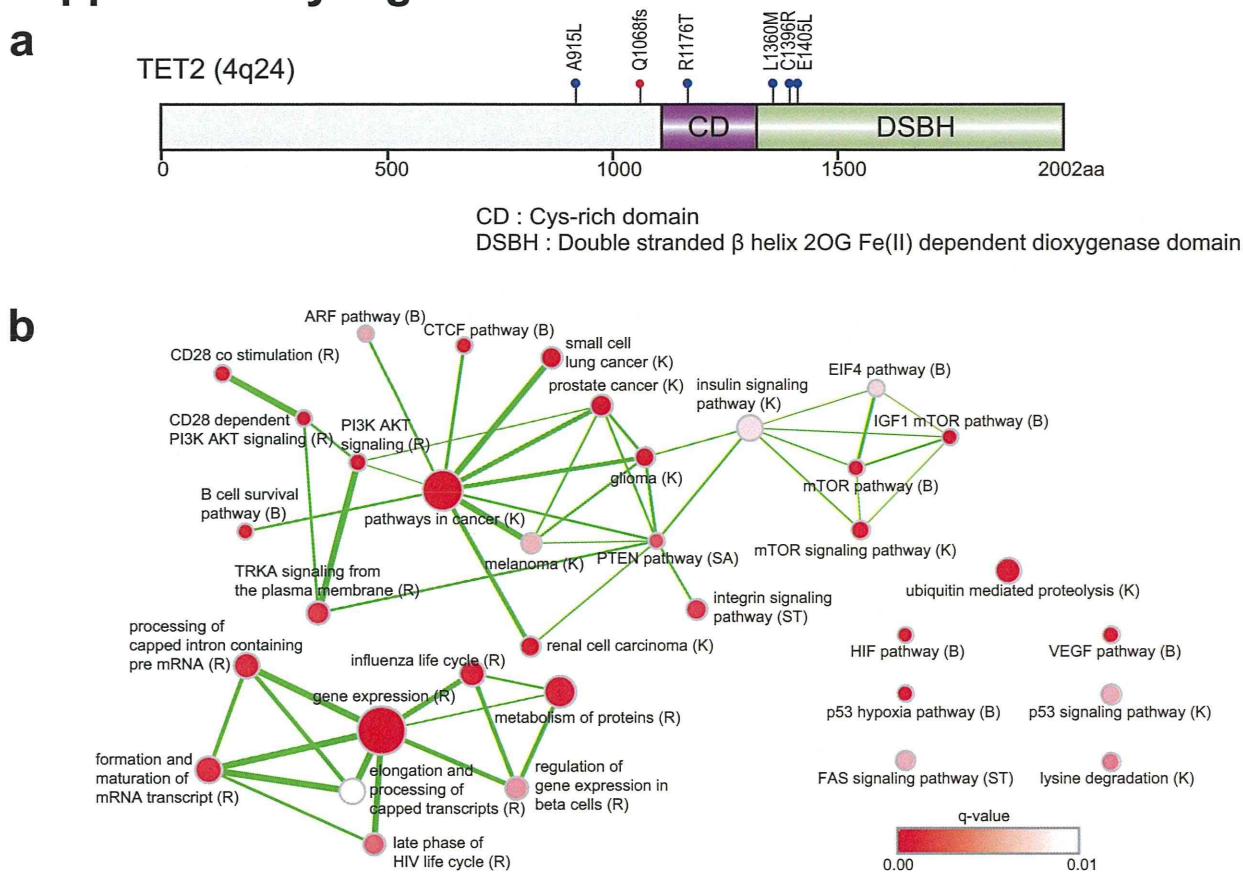
Supplementary Figure 13



Significantly mutated genes/pathways in 106 exome cases

(**a**) TET2 mutations in ccRCC. Type and position of TET2 mutations are indicated. (**b**) Significantly mutated pathways are shown in red circles based on the significance level (*q* values) as indicated by the color gradient. (B):Biocarta (K):KEGG (R):Reactome (ST):Signaling Transduction KE (**c**) Somatic mutations observed in the apparatus for mRNA processing.

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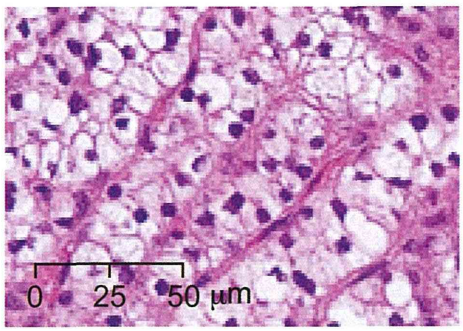
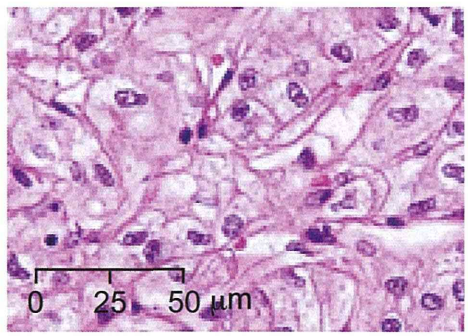
Supplementary Figure 14

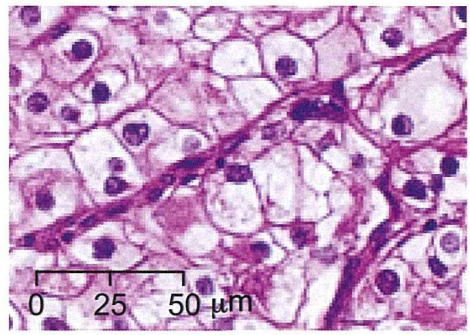
KEAP1 mutation



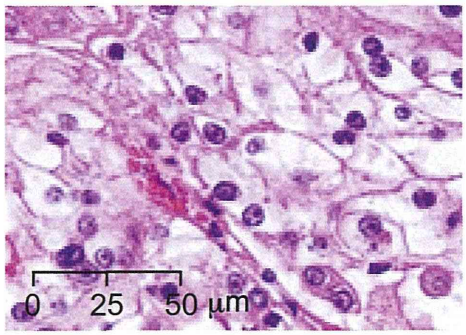
ccRCC-11



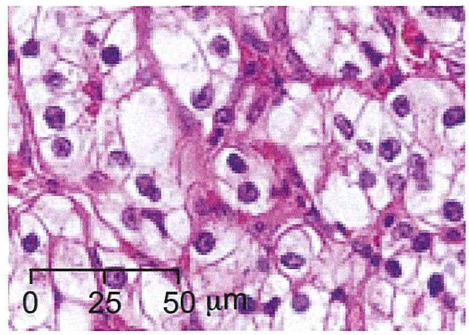
ccRCC-15



ccRCC-34

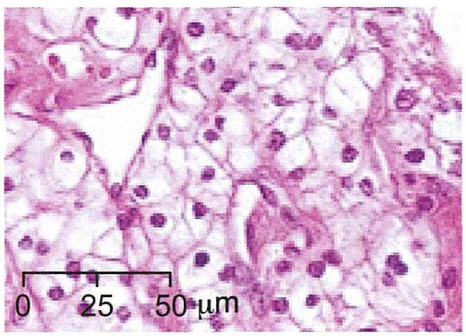


ccRCC-46



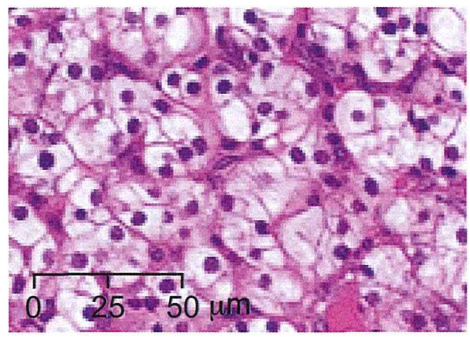
ccRCC-51

NRF2 mutation



ccRCC-82

CUL3 mutation



ccRCC-18

Histologies of tumors having *KEAP1/NRF2/CUL3* mutations.
All cases were confirmed as clear cell RCC with no papillary components on HE staining.

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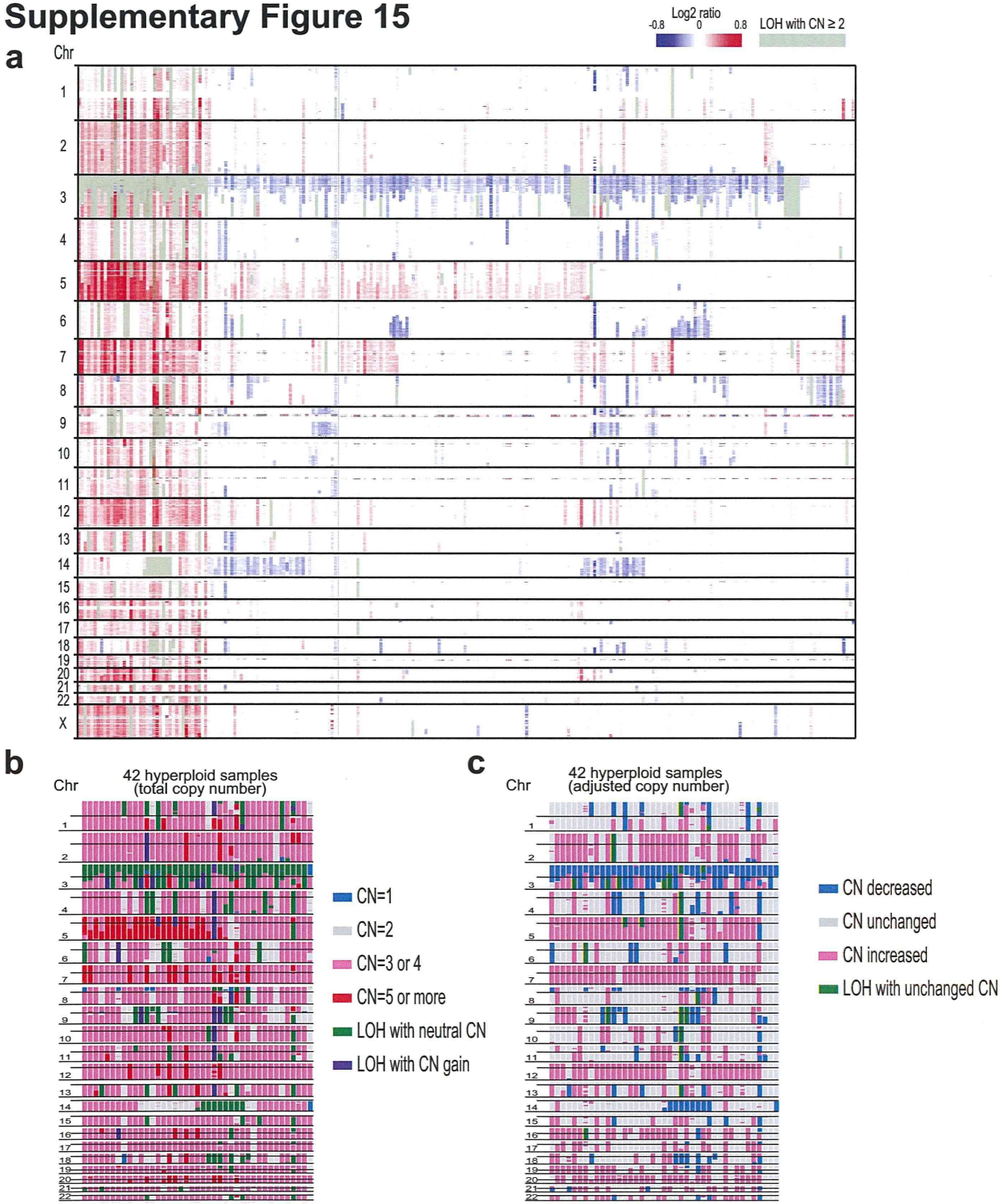
Supplementary Figure 15

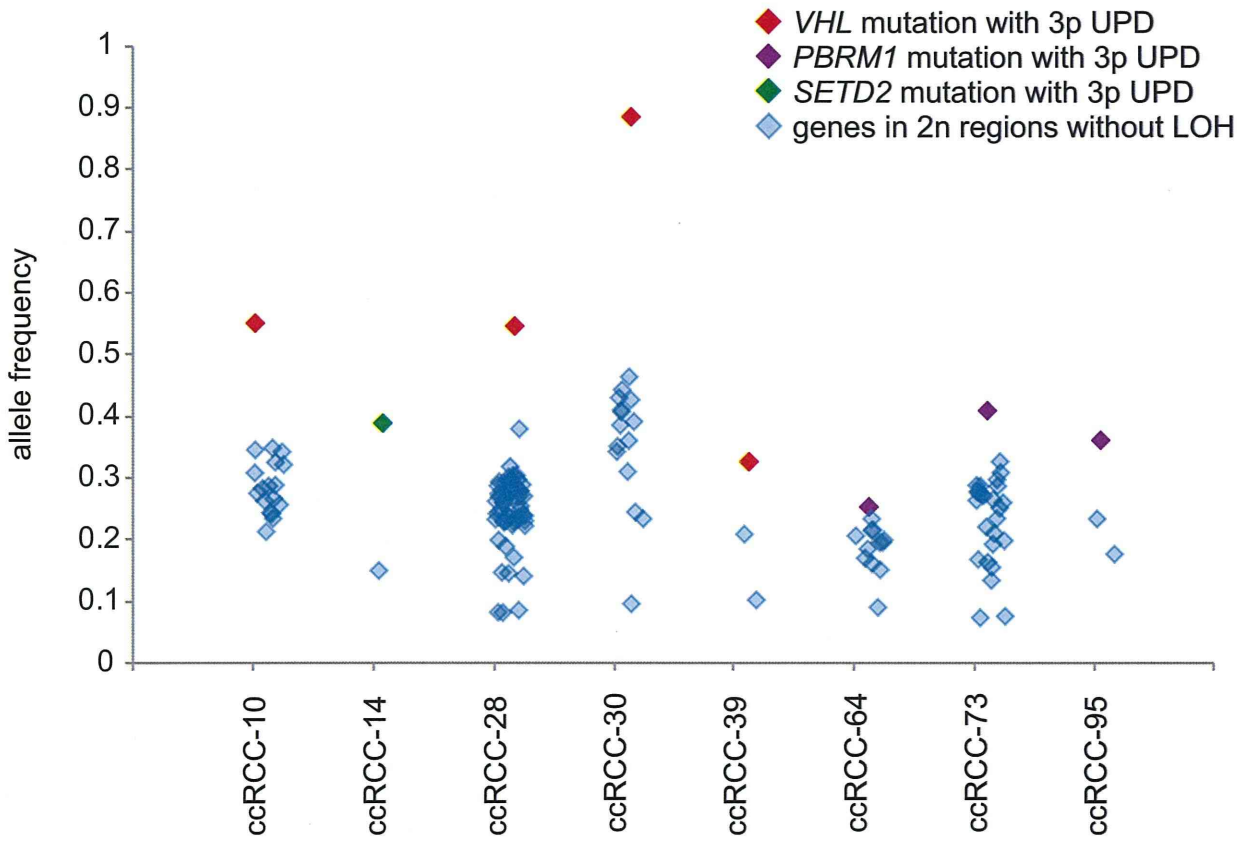


Copy number profiles of 240 ccRCC specimens

(**a**) Genomic copy number determined by SNP array analysis are shown by a color gradient based on CNAG output for 240 ccRCC specimens. Regions showing copy neutral LOH are overlayed in light green. Samples were clustered based on major copy number lesions, including hyperploidy, 3p loss, 5q gain, 14q LOH, 9p LOH and other abnormalities. (**b**) Genomic copy numbers inferred by HMM based analysis of 42 hyperploid samples are shown by the indicated colors. (**c**) The copy number plots for hyperploid cases (b) were transformed by calculating relative copy numbers to the base line copy number (=3), in which the copy number status was either increased (CN > 3, pink), decreased (CN < 3, blue), or unchanged (CN = 3, gray). This relative copy number profile was an essentially identical to that for diploid samples (a), characterized by losses of 3p, 4q, 6q, 9p,9q, 14q and gains of 5q and 7q, suggesting that these hyperploid tumors were most likely progressed from diploid tumors as a relatively late event.

Nature Genetics: doi:10.1038/ng.2699

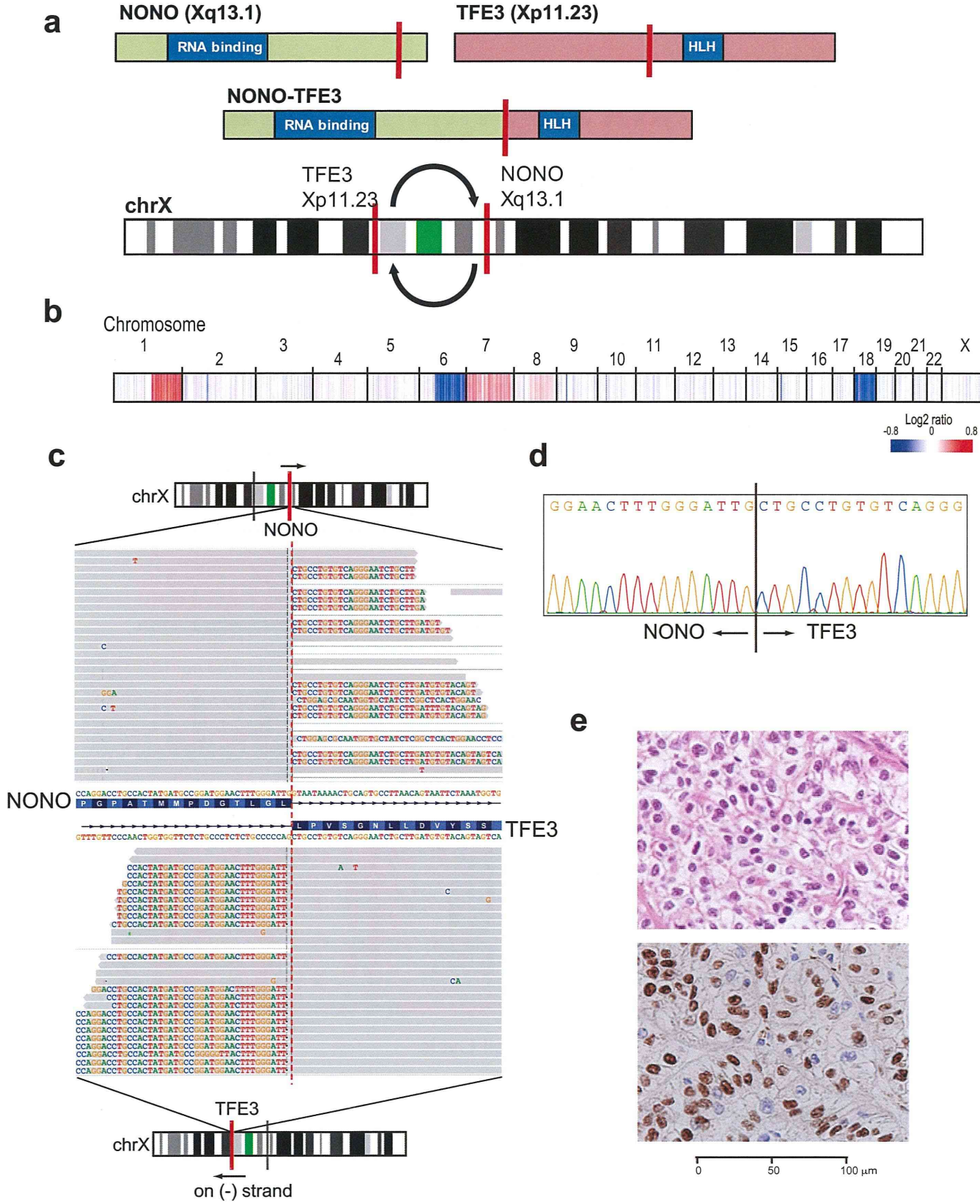
Supplementary Figure 16



Higher allele frequencies of mutations in the 3p target genes in cases with 3p UPD. 8 out of 25 cases with 3p UPD had mutations in either *VHL*, *PBRM1* or *SETD2*, which were analyzed by enough depths (> 50x) with whole exome sequencing for accurate estimation of allele frequency and also had one or more mutations in copy number 2n regions. Allele frequencies of 3p target in 3p UPD were higher than those of other mutations within 2n regions in all 3p UPD cases.

Nature Genetics: doi:10.1038/ng.2699

Supplementary Figure 17



***NONO-TFE3* fusion transcript**

NONO-TFE3 fusion transcript was found in single case (**a**), in which copy number alterations characteristic to ccRCC such as 3p LOH and 5q gain were lacked (**b**). The junction sequence of fusion transcript was showed with IGV viewer (**c**) and confirmed with sanger sequencing (**d**). (**e**) The tumor was positive for TFE3 in IHC (lower panel) but hardly distinguishable from other ccRCC cases on HE staining (upper panel).

Nature Genetics: doi:10.1038/ng.2699