Supplementary Information for:

Comprehensive identification of mutational cancer driver genes across 12 tumor types

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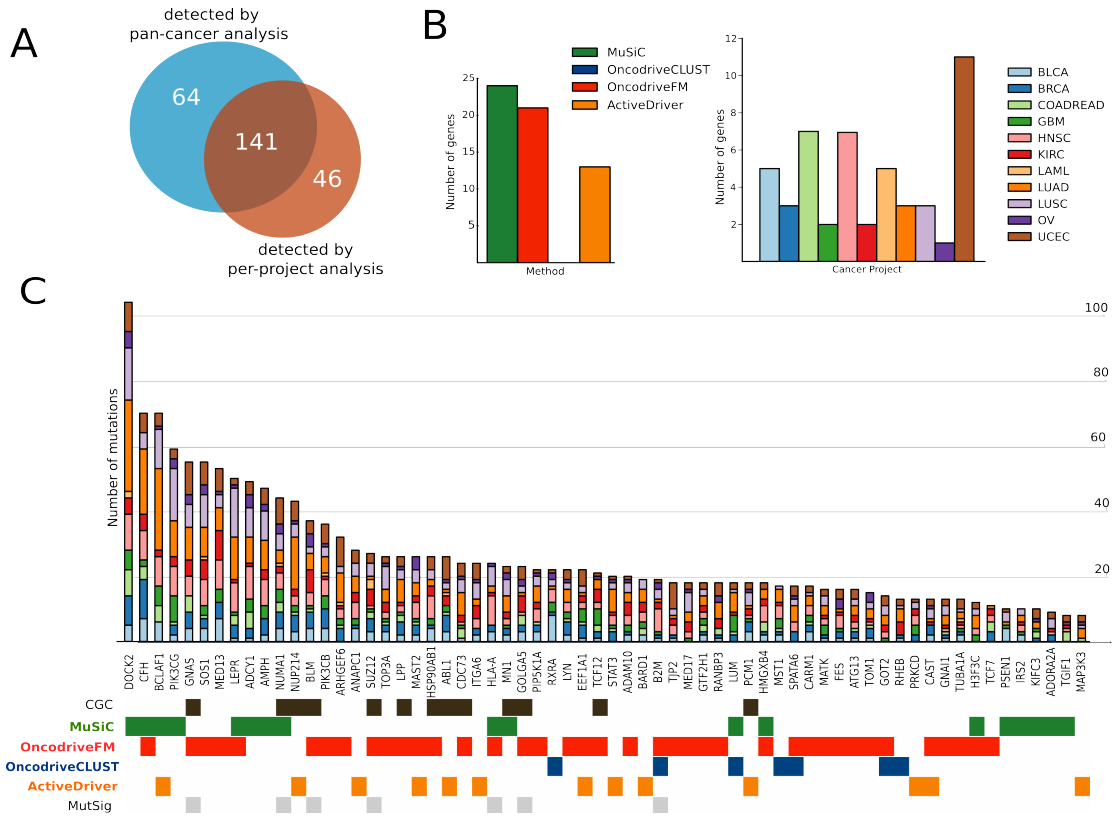
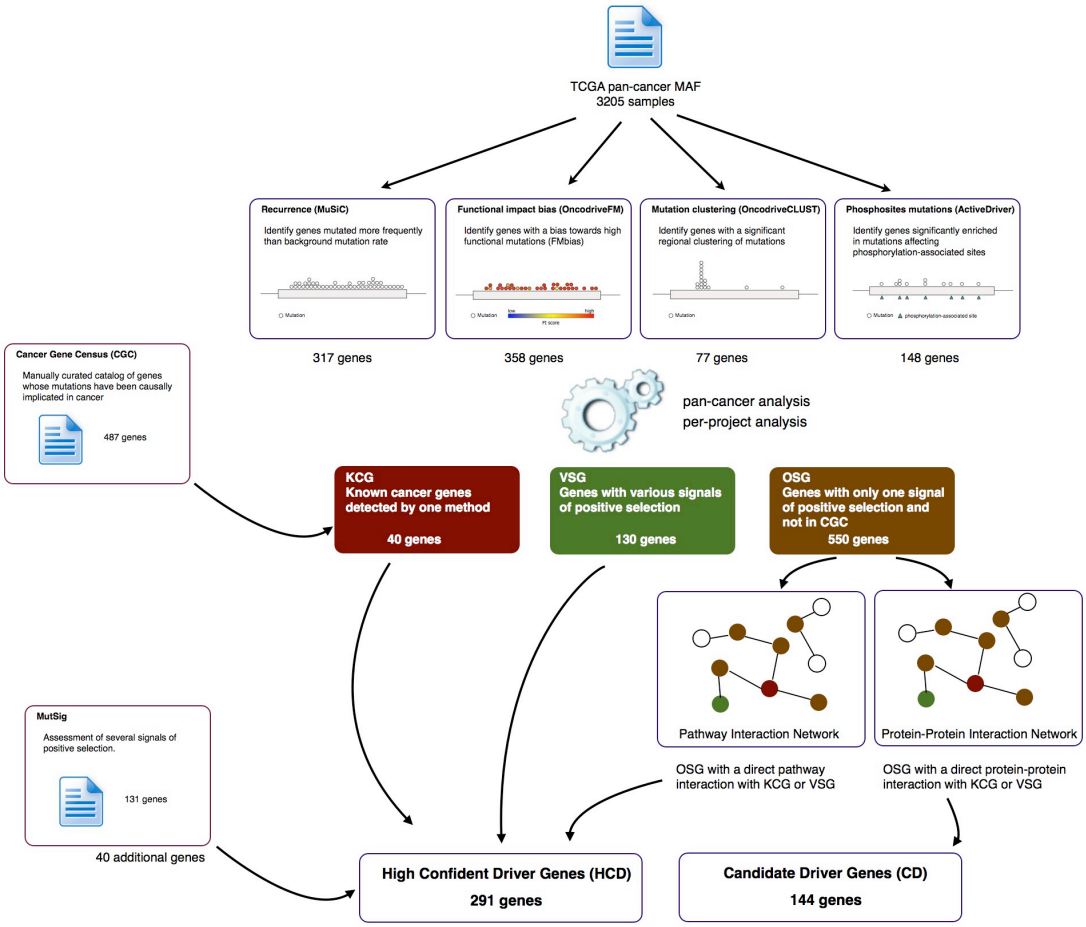


Supplementary Figure 1. Results of combining the pan-cancer analysis and the per-project analyses.

A) Venn diagram comparing the HCDs retrieved by the pan-cancer analysis with those obtained by any of the per-project analyses. Note that the increase in statistical power emerging from the combination of the 3205 samples from the 12 tumor types in pan-cancer permits the detection of 64 HCDs that don't appear in any per-project analysis. They are probably below the threshold of detections of the methods in the per-project analyses, because they are mutated at very low frequencies in each tumor type, but rather ubiquitously mutated across tumor types. (This is shown in panel C.) Pooling all samples together thus allows them to reach the critical point at which methods are able to analyze them and nominate them as likely drivers.

B) Details of the 46 HCDs retrieved only by per-project analyses: the histogram at the left depicts the number of these genes that were selected by each method, and the histogram at the right depicts in which cancer project they were identified. Note that they can be selected by more than one method and/or in more than one per-project analysis. Mutations in these genes are concentrated in one or few tumor types so that when they are probed for the signals of positive selection across the 3205 pan-cancer samples, these mutations are probably diluted with respect to the methods' backgrounds.

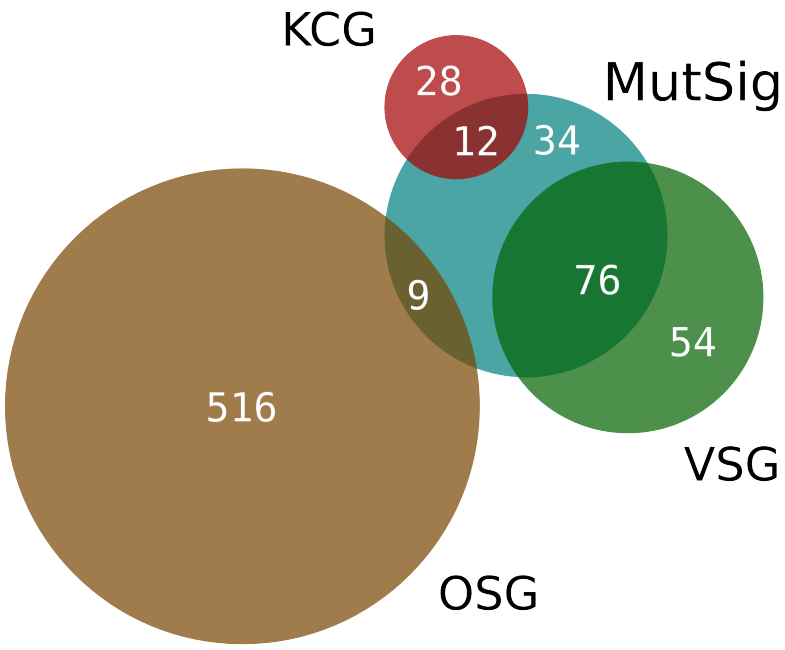
C) Histogram of the number of samples with PAMs in each cancer type for the 64 HCDs retrieved uniquely by the pan-cancer analysis approach and the signals of positive selection they showed. Interestingly, very few of these genes are included in the cancer genes census, probably because their low recurrence had allowed them to remain elusive to analyses with less statistical power.



Supplementary Figure 2. General flowchart of the approach taken to identify putative mutational cancer drivers from the combination of four complementary approaches.

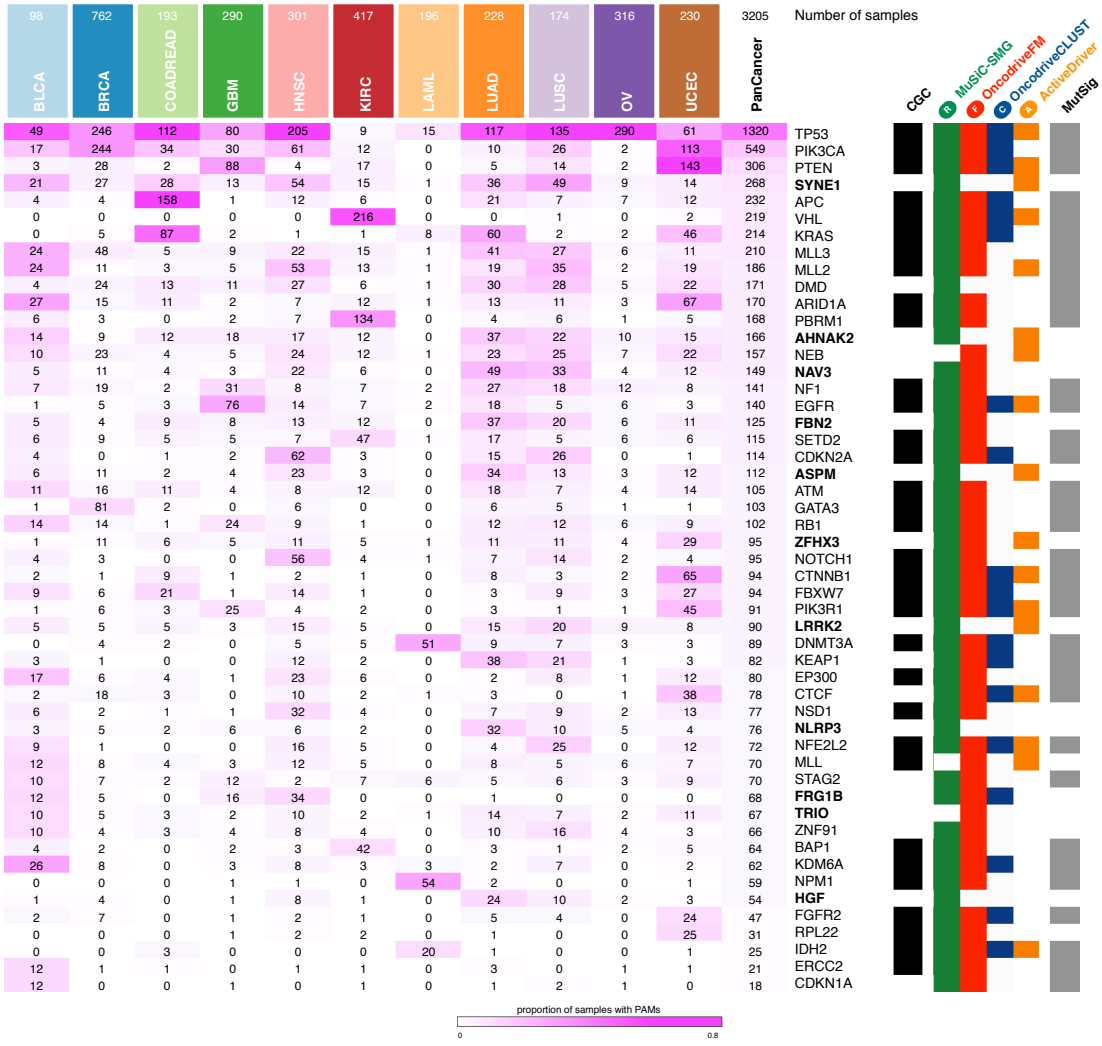
For further details, see the Methods section.

Briefly, mutations detected in genes across the 3205 samples of the 12 tumor types in pan-cancer were analyzed with four complementary methods (MuSiC, OncodriveFM, OncodriveCLUST, and ActiveDriver). The aim was to detected genes with signals of being positively selected upon mutations in these tumor samples. Each method gave as output a prioritized list of driver candidates cut at different lengths as explained in Supplementary Figure 1A. The genes in the 48 lists generated after running the five methods on the pan-cancer dataset and on each tumor type's dataset separately –after careful expression filtering– were integrated into three short lists. Theses were: the genes with various signals of positive selection (VSGs), the known cancer genes with one signal of positive selection (KCGs), and the genes with one signal of positive selection not in the cancer gene census (OSGs). The former two categories integrated the High-confidence drivers (HCD) list. Genes in the latter category were probed for functional interactions with HCDs and those with such functional connections were rescued and added to the HCD list. On the other hand, OSGs involved in protein-protein interactions with HCDs were placed in a separate group of Candidate Drivers, or CDs. Finally, 40 genes detected by MutSig as significantly mutated which were not previously in the HCD list were included within it for completion.



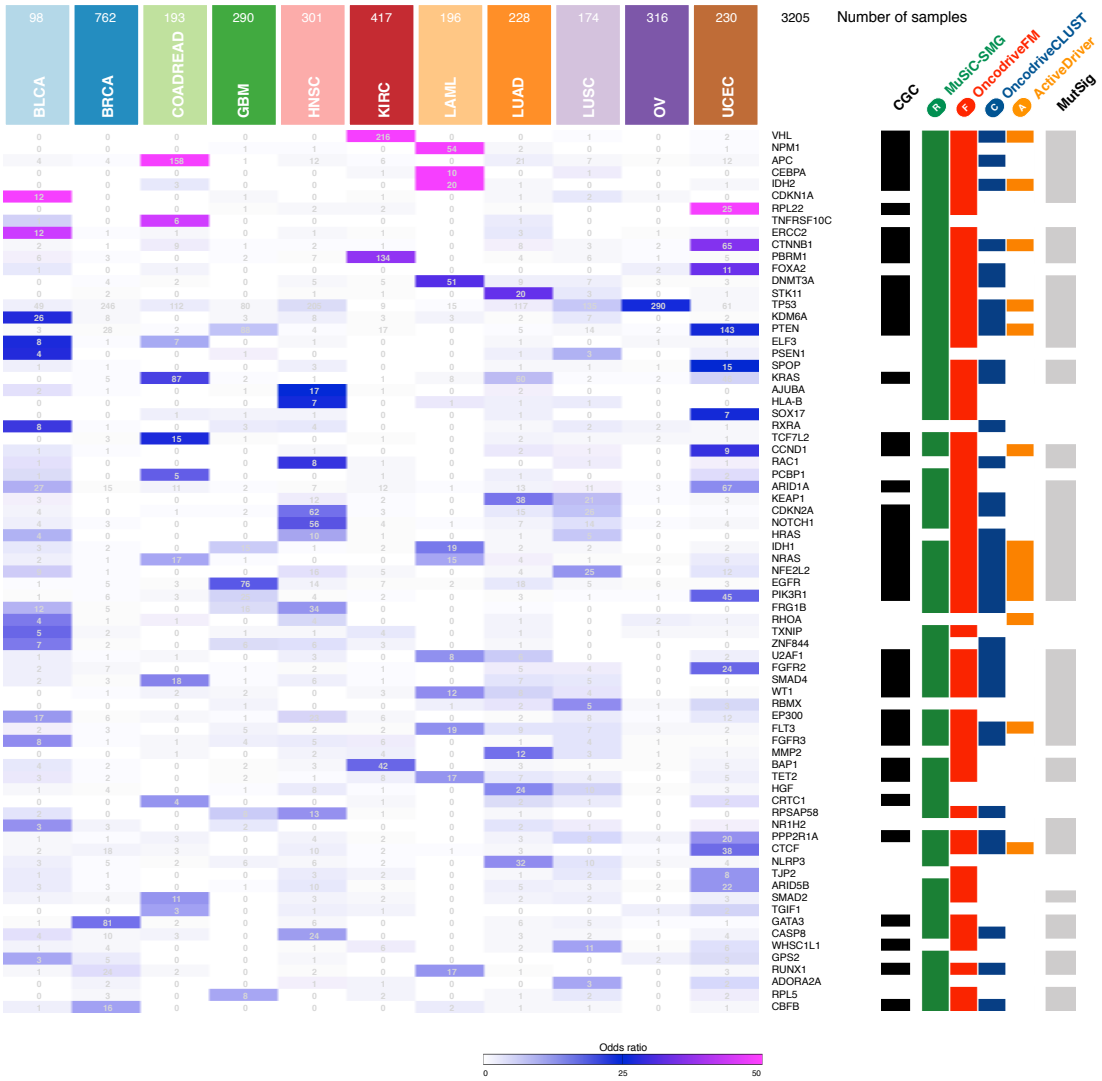
Supplementary Figure 3. Venn diagram showing the overlap between the genes selected by MutSig and those selected by the initial combination of the four other methods.

The numbers represent the results of the pan-cancer analysis and each per-project analyses. The VSG list contains genes exhibiting various signals of positive selection; The KGC list contains known cancer genes (i.e. those included in the Cancer Gene Census) that showed one signal of positive selection; and the OSG list includes the remaining genes in which only one signal of positive selection was identified and are not in the CGC. Six genes that had been nominated as CDs by our approach (see Supplementary Figure 3) were identified by MutSig as significantly mutated and thus added to the HCD list. Thirty-four others detected by MutSig and not in OSG list were also added to the HCD list. Therefore, in summary, forty genes highlighted as likely drivers by MutSig were incorporated to our catalog of HCDs, as explained in the main paper and in the Methods section.



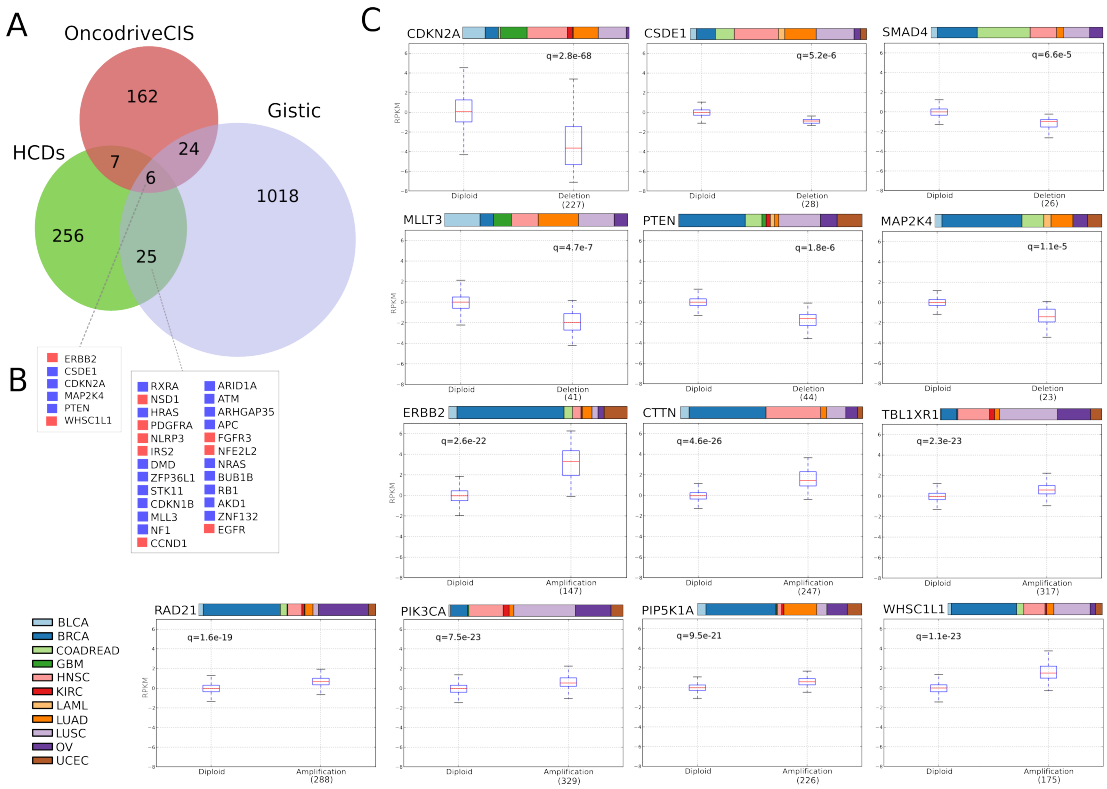
Supplementary Figure 4. 51 HCDs bearing PAMs in more than 10% of samples of at least one cancer type. The number in the heat-map indicates the number of samples with PAMs in the gene and the color indicates the frequency. The 51 genes are ordered according to the overall frequency in the whole dataset. The annotations at the right side indicate if the gene is in the Cancer Gene Census (CGC), if it is detected by MuSiC, OncodriveFM, OncodriveCLUST and/or MuSiC, and if the gene is identified as significantly mutated by MutSig. ‘Novel’ drivers discussed at length in Supplementary Table 4 are written in bold.

Supplementary Figure 5

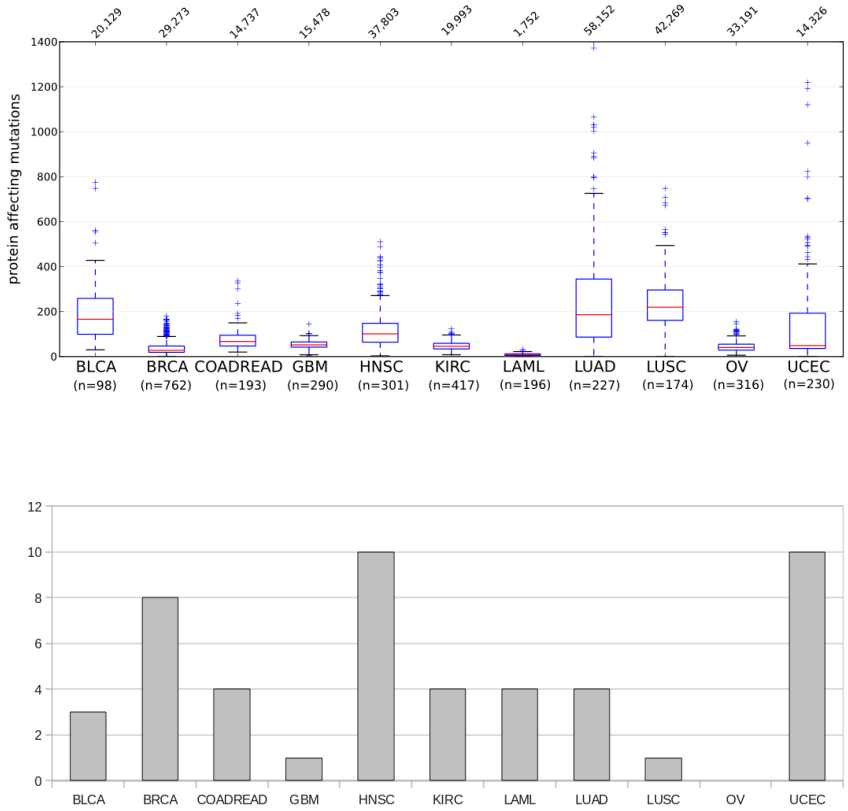


Supplementary Figure 5. Top 75 HCDs showing clearer preference for acting as mutational drivers in certain tumor types according to odds ratio calculation. The numbers in the heatmap indicate the number of samples with PAMs in the gene and the color indicates the Fisher's odds ratio. The 75 genes are ordered according to the overall frequency in the whole dataset. The annotations at the right side indicate if the gene is in the Cancer Gene Census (CGC), if it is detected by MuSiC, OncodriveFM, OncodriveCLUST and/or MuSiC, and if the gene is identified as significantly mutated by MutSig.

Supplementary Figure 6



Supplemental Figure 6. A) Venn diagram showing HCDs that were also selected as recurrently altered according to Gistic and/or biased towards larger misregulation according to the OncodriveCIS analysis of the pan-cancer data set. For the latter, we have taken the 100 top-ranking genes due to amplifications and deletions; these lists exhibited a significant enrichment of HCDs (Fisher's p<1e-04). B) List of genes selected by Gistic within a region either significantly amplified (red squares) or deleted (blue squares). C) Expression boxplots of the HCDs selected by OncodriveCIS depending on their CNAs. Top color bars depict the proportion of CNAs observed in each cancer type.



Supplemental Figure 7. Upper panel: Boxplot of the protein affecting mutations per cancer project. Numbers above the plot depict the total number of mutations in each of these projects, whereas numbers below the plot -between parenthesis- depict the number of samples.
Lower panel: Number of drivers that are predominantly mutated in each tumor type, as identified by following the criteria defined in the Methods section.

Supplementary Table 1. Details of the datasets used for the analysis, including the number of samples of each cancer site, the number of PAMs, the number of PAMs in HCDs and the number of samples with PAMs in at least one HCD.

Project Name	Tumor Type	Number of samples	Median and interquartil ranges of protein affecting mutations (PAMs) in all genes per sample	Median and interquartil ranges of protein affecting mutations (PAMs) in HCDs per sample	Number of samples (and proportion) with PAMs in at least one HCD
BLCA	Bladder Urothelial Carcinoma	98	160 (157)	9.5 (7.5)	98 (1.0)
BRCA	Breast invasive carcinoma	762	28 (27)	3 (2)	710 (0.93)
COADREAD	Colon and Rectum adenocarcinoma	193	65 (47)	5 (2)	193 (1.0)
GBM	Glioblastoma multiforme	290	51 (23)	4 (3)	272 (0.94)
HNSC	Head and Neck squamous cell carcinoma	301	97 (79)	6 (5)	299 (0.99)
KIRC	Kidney renal clear cell carcinoma	417	45 (24)	3 (3)	393 (0.94)
LAML	Acute Myeloid Leukemia	193	8 (7)	2 (3)	165 (0.85)
LUAD	Lung adenocarcinoma	226	183 (248)	9 (8)	221 (0.98)
LUSC	Lung squamous cell carcinoma	174	209 (123)	9 (7)	172 (0.99)
OV	Ovarian serous cystadenocarcinoma	316	40 (276)	2 (2)	312 (0.99)
UCEC	Uterine Corpus Endometrioid Carcinoma	230	48 (153)	6 (9)	228 (0.99)

Supplementary Table 2. List of HCDs and CDs with their signals of positive selection annotated. This table is available as tab separated text file in Synapse (**syn1962006**).

Supplementary Table 3. Highly enriched (FDR < 0.001) biological processes for HCDs.

After constructing the Functional Interaction network as explained in Methods, it was partitioned into clusters employing the Reactome FI plugin and the resulting clusters were probed for enrichment of Biological Processes Gene Ontologies terms. The table presents selected highly enriched Biological Processes Gene Ontologies terms grouped into five broad modules of cellular functions.

Supplementary Table 3

Broad	GOBP term	Gene fraction	Genes in	HCDs	P value	FDR	HCDs names
mRNA	nuclear mRNA splicing, via	0.0119	105	8	0	<1.000e-03	SF3B1,PRPF8,PCBP1,U2AF1,CCAR1,DHX9,R
	RNA splicing	0.0208	184	8	0	<2.500e-04	NONO,SF3B1,PRPF8,U2AF1,PABPC1,PPP2R
	mRNA transport	0.0058	51	5	0	<2.000e-04	NUP98,NUP93,NUP214,RANBP2,TPR
chromatin	chromatin modification	0.0136	120	15	0	<1.000e-03	ARID1A,SUZ12,BCOR,MLL,NCOR1,EZH2,TB
	histone methylation	0.0006	5	3	0	5.63E-04	SUZ12,CARM1,NSD1
Cell cycle/	G1/S transition of mitotic	0.0041	36	8	0	<1.667e-04	CDKN2A,CDKN2C,CUL1,CDKN1A,CDKN1B,
	cell cycle arrest	0.0087	77	10	0	<1.429e-04	CDKN2A,CDKN2C,CUL1,STK11,CDKN1A,CD
	negative regulation of cell	0.0111	98	8	0	6.15E-04	WT1,TSC2,TP53,RB1,VHL,NF1
	response to DNA damage	0.0208	184	11	0	<1.000e-03	BLM,TP53BP1,BRCA2,CHEK2,ATR,WRN,AT
	DNA repair	0.0135	119	6	0	<5.000e-04	BLM,TP53BP1,ATR,ATM,MDC1,FANCA
	double-strand break repair	0.0017	15	3	0	<3.333e-04	BLM,BRCA2,BRCA1
	replication fork protection	0.0002	2	2	0	5.00E-04	BLM,BRCA2
	replication fork processing	0.0002	2	2	0	5.00E-04	BLM,WRN
Cell	androgen receptor	0.0038	34	8	0	<2.000e-04	CTNNB1,MED12,ARID1A,MED13,MED17,AR,
	negative regulation of cell	0.0058	51	8	0	<1.111e-04	CDKN2A,CDKN2C,SMAD4,CDKN1A,CDKN1B
	negative regulation of cell	0.0214	189	12	0	<9.091e-05	CDKN2A,CDKN2C,CUL1,STK11,AXIN2,SMAD
	protein amino acid	0.0428	379	13	0	<1.000e-03	PIK3CA,MATK,PIK3CG,SGK1,LYN,BRAF,PRK
	phosphoinositide	0.0014	12	4	0	1.00E-03	PIK3CA,PIK3CG,PIK3CB,PIK3R1
	peptidyl-tyrosine	0.0019	17	4	0	4.00E-04	FES,PDGFRA,KIT,ABL1
	positive regulation of cell	0.0188	166	8	0	5.71E-04	HRAS,MATK,LYN,LIFR,KIT,KRAS,FLT3,NRAS
	phosphoinositide-mediated	0.0032	28	4	0	8.18E-04	PIK3CA,PIK3CG,PIK3CB,ERBB2
	transmembrane receptor	0.0078	69	5	0	9.29E-04	NCOA4,ADORA2A,ERBB2,KIT,FLT3
	positive regulation of MAP	0.0014	12	3	0	9.33E-04	EGFR,ERBB2,KIT
Cell	positive regulation of cell	30	4	0.0034	0	2.50E-04	EGFR,IRS2,PDGFRA,PIK3R1
	Wnt receptor signaling	10	3	0.0011	0.0002	4.43E-03	CTNNB1,TCF7L2,APC

Supplementary Table 4. Information from literature about the function and previous evidence of cancer involvement of a set of novel mutational drivers identified in this study. Genes discussed in the Table are shown as examples in the manuscript and Figures 3 and 4.

Supplementary Table 4

Gene name	Description	Evidences from function (taken from GeneCards; http://www.genecards.org and literature)	Evidences of involvement in cancer	Comments
Mutated in more than 10% of samples in at least one tumor type				
SYNE1	Spectrin Repeat Containing, Nuclear Envelope 1	Implicated in the regulation of nuclear polarity (S. E. Williams et al. 2011), a process that operates upstream of NOTCH1 in squamous epithelia	Frequently mutated in head and neck squamous cell carcinomas (Stransky et al. 2011)	
AHNAK2	AHNAK Nucleoprotein 2	AHNAK/Desmoyokin is a giant protein, recently linked to reorganization of the actin cytoskeleton, cellular migration and invasion.	Tumoral AHNAK overexpression is significantly associated with poor survival in laryngeal carcinoma (Dumitru et al. 2013) Ahnak protein was shown to function as the signalling scaffold interacting with the multiple protein complex of Erk, PAK, and p21-activated kinase-interacting exchange factor β. Ahnak protein plays an important scaffolding function connecting Erk and Rac activation in PDGF-dependent migration of ASMC (H. J. Lim et al. 2013).	
NAV3	Neuron Navigator 3	This gene belongs to the neuron navigator family and is expressed predominantly in the nervous system.	NAV3 copy number changes are frequent in CRC and in adenomas, and upregulation of IL23R, following NAV3 silencing, strongly correlates with Dukes' staging and lymph node metastases. This suggests that NAV3 has a role in linking tissue inflammation to cancer development in the colon (Carlsson et al. 2012).	
FBN2	Fibrillin 2	The protein encoded by this gene is a component of connective tissue microfibrils and may be involved in elastic fiber assembly. Mutations in this gene cause congenital contractural arachnodactyly. Regulates osteoblast maturation by controlling TGF-beta bioavailability	It is a tumor suppressor gene silenced by aberrant DNA methylation in renal cell carcinoma. It may contribute to the dysregulation of the complex network of signalling pathways regulated by TGF-b (Kikuyama et al. 2012; Morris et al. 2011)	

		and calibrating TGF-beta and BMP levels, respectively.		
ASPM	Asp (Abnormal Spindle) Homolog, Microcephaly Associated (Drosophila)	Probable role in mitotic spindle regulation and coordination of mitotic processes. May have a preferential role in regulating neurogenesis.	Identified as implicated in metastatic progression in Melanomas. Functional assay validated its pro-invasion activities in human melanoma cells (Kabbarah et al. 2010) ASPM inhibition by siRNA-mediated knockdown was found to inhibit tumor cell proliferation and neural stem cell proliferation in glioma cells, further supporting its role as a potential molecular cancer target (Horvath et al. 2006)	
ZFHX3	Zinc Finger Homeobox 3	Transcriptional repressor. It inhibits the enhancer element of the AFP gene by binding to its AT-rich core sequence. Regulator of myoblasts differentiation through the binding to the AT-rich sequence of MYF6 promoter and promoter repression. Down-regulates the MUC5AC promoter in gastric cancer	ATBF1 encodes a transcription factor that negatively regulates AFP and MYB but transactivates CDKN1A. Frequent somatic mutations of this gene were reported in human prostate cancer (X. Sun et al. 2005)	Known cancer gene
LRRK2	Leucine-Rich Repeat Kinase 2	May play a role in the phosphorylation of proteins central to Parkinson's disease. Phosphorylates PRDX3. May also have GTPase activity. Positively regulates autophagy through a calcium-dependent activation of the CaMKK/AMPK signaling pathway. The process involves activation of nicotinic acid adenine dinucleotide phosphate (NAADP) receptors, increase in lysosomal pH, and calcium release from lysosomes.	Dominant mutations in the LRRK2 gene are the most common cause of familial PD (Parkinson's disease). Functionally implicated in autophagy	
NLRP3		May function as an inducer of apoptosis. Interacts selectively with ASC and this complex may function as an upstream activator of NF-kappa-B signaling. Inhibits		

		TNF-alpha induced activation and nuclear translocation of RELA/NFKB p65. Also inhibits transcriptional activity of RELA. Activates caspase-1 in response to a number of triggers including bacterial or viral infection which leads to processing and release of IL1B and IL18		
FRG1B	FSHD Region Gene 1 Family, Member B	?		
TRIO	Trio Rho Guanine Nucleotide Exchange Factor	Promotes the exchange of GDP by GTP. Together with leukocyte antigen-related (LAR) protein, it could play a role in coordinating cell-matrix and cytoskeletal rearrangements necessary for cell migration and cell growth.	Rho-GEFs Guanine nucleotide exchange factors (GEFs) that promotes GTP loading onto the guanosine triphosphatases (GTPases) Rho and Rac, prominent players in cancer progression.	
ZNF91	Zinc Finger Protein 91	The ZNF91 gene encodes a zinc finger protein of the KRAB (Kruppel-associated box) subfamily (Bellefroid et al. 1991; Bellefroid et al. 1993).		
HGF	Hepatocyte Growth Factor	Potent mitogen for mature parenchymal hepatocyte cells, seems to be a hepatotrophic factor, and acts as growth factor for a broad spectrum of tissues and cell types. Activating ligand for the receptor tyrosine kinase MET by binding to it and promoting its dimerization.		
Exemplary lowly recurrent putative novel drivers				
ACVR1B	Activin A Receptor, Type II-Like Kinase	Member of the TGF-beta superfamily of receptors. Fosforilates SMAD proteins SMAD2 and SMAD3, on serine residues of the C-terminal tail (Bernard and Tran, 2013).	Mutations in ACVR1B significantly enhanced the migratory ability of cell lines. In a xenograft model, histological analysis revealed that the expression of Snail, a cell-adhesion-suppressing transcription factor, was dramatically increased in ALVA-ActRIBCA tumors, indicating epithelial mesenchymal	

			transition (EMT). Finally, mice bearing ALVA-ActRIBCA cells developed multiple lymph node metastases (Nomura et al. 2013).	
CDKN1A	Cyclin-Dependent Kinase Inhibitor 1A	Intermediate of the role of TP53 as inhibitor of cellular proliferation after DNA damage. Inhibits cyclin-dependent kinase activity, preventing phosphorylation of cyclin-dependent kinase substrates and blocks cell cycle (Insinga et al. 2013).	Plays a partial role in induced pluripotent stem cells formation probably by slowing cell division. Polymorphisms in this gene have been associated to increased risk of several cancers (F. Liu et al. 2013; Zhongqiu Wang et al. 2012; Ying et al. 2011). It's also been identified as transcriptionally missregulated in tumors (Dehennaut et al. 2013).	Cell Cycle/DNA repair module in Figure 2A. Cell cycle pathway in Figure 3A.
CDKN1B	Cyclin-Dependent Kinase Inhibitor 1B	Binds to and prevents the activation of cyclin E-CDK2 or cyclin D-CDK4 complexes, and thus controls the cell cycle progression at G1 (J. Lee & Sung Soo Kim 2009).	Its downregulation is often correlated with poor prognosis in several types of human cancers. The protein can also be functionally inactivated by cytoplasmic localization or by phosphorylation, but it's seen only rarely mutated(Carracedo et al. 2008; C. Yao et al. 2008; M. Sun et al. 2012; Kruck et al. 2012).	Cell Cycle/DNA repair module in Figure 2A. Cell cycle pathway in Figure 3A.
ATR	Ataxia Telangiectasia And Rad3 Related	Cell cycle checkpoint gene required for cell cycle arrest and DNA damage repair in response to DNA damage. This kinase has been shown to phosphorylate checkpoint kinase CHK1, checkpoint proteins RAD17, and RAD9, as well as tumor suppressor protein BRCA1 (Dart et al. 2004).	Polymorphisms in this gene have been associated to increased cancer susceptibility (Heikkinen et al. 2005; Zienolddiny et al. 2006) and somatic mutations have been linked to DNA repair defective cancers with hypermutator phenotypes (Zighelboim et al. 2009).	Cell Cycle/DNA repair module in Figure 2A. Missmatch repair, Homologous recombination and Cell cycle pathways in Figure 3A.
FOXA1	Forkhead Box A1	Transcription factor involved in embryonic development, establishment of tissue-specific gene expression and regulation of gene expression in differentiated tissues. Is thought to act as a 'pioneer' factor, opening the compacted chromatin for other proteins (Bernardo & Keri 2012).	Its aberrant expression in several tissue types transcriptionally alters several known cancer drivers, thus promoting tumorigenesis (Williamson et al. 2006; Imamura et al. 2012; Deutsch et al. 2012).	Cell signaling/proliferation module in Figure 2A. PI3K and General transcription pathways in Figure 3A.
FOXA2	Forkhead Box A2	Transcription factor involved in embryonic development,	Its expression is known to be missregulated in several malignancies (Mirosevich et al.	Cell signaling/proliferation module in Figure 2A.

		establishment of tissue-specific gene expression and regulation of gene expression in differentiated tissues. Is thought to act as a 'pioneer' factor opening the compacted chromatin for other proteins (Rausa et al. 2003).	2006; M. Liu et al. 2012). It's been linked to promotion of metastases in some tumor types (Lehner et al. 2007).	PI3K and General transcription pathways in Figure 3A.
STAG2	Stromal Antigen 2	Component of cohesin complex, a complex required for the cohesion of sister chromatids after DNA replication (Sumara et al. 2000).	Upon somatic mutations or deletions, STAG2 is known to be involved both in leukemias and solid cancers through the development of aneuploidy (Chung et al. 2012; M S Kim et al. 2012; Solomon et al. 2011).	Cell Cycle/DNA repair module in Figure 2A. Cell cycle pathway in Figure 3A.
PIK3CB	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase, Catalytic Subunit Beta	Encodes an isoform of the catalytic subunit of phosphoinositide 3-kinase (PI3K). These kinases are important in signaling pathways involving receptors on the outer membrane of eukaryotic cells and are named for their catalytic subunit. The encoded protein is the catalytic subunit for PI3Kbeta. PI3K regulate several essential cellular processes, such as cell growth and cell cycle entry (Kumar et al. 2011; Marqués et al. 2008).	While it's been shown to harbor somatic mutations implicated in tumorigenesis in some cancer types. PIK3CB de-regulation is very important in PTEN-deficient tumors, where it directly affects cell growth (Hill et al. 2010; Wee et al. 2008).	Cell signaling/proliferation module in Figure 2A. PI3K pathway in Figure 3A.
PIK3CG	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase, Catalytic Subunit Gamma	Encodes a protein that belongs to the PI3/PI4-kinase family of proteins. The gene product is an enzyme that phosphorylates phosphoinositides on the 3-hydroxyl group of the inositol ring. It is an important modulator of extracellular signals, including those elicited by E-cadherin-mediated cell-cell adhesion, which plays an important role in maintenance of the structural and functional integrity of epithelia (Vogelmann et al. 2005).	Both, genetic and epigenetic alterations of PIK3CB have been linked to the progression of several cancer types. Specifically, it has been related with cancer invasion, metastasis, and poor cell differentiation (Sasaki et al. 2000; Semba et al. 2002).	Cell signaling/proliferation module in Figure 2A. PI3K pathway in Figure 3A.
MED13	Mediator	Component of the	MED13 is targeted for	Cell

	complex subunit 13	Mediator complex, a coactivator involved in the regulated transcription of nearly all RNA polymerase II-dependent genes. Mediator functions as a bridge to convey information from gene-specific regulatory proteins to the basal RNA polymerase II transcription machinery (Y. K. Kang et al. 2002; Gustafsson & Samuelsson 2001; Davis et al. 2013).	degradation by the known tumor suppressor FBXW7. Alterations in both FBXW7 and MED13 –for example through amplification in several cancers (Paz et al. 2007)– are thus hypothesized to be related to oncogenesis and tumor progression (Davis et al. 2013).	signaling/proliferation module in Figure 2A. General transcription pathway in Figure 3A.
MED17	mediator complex subunit 17	Component of the Mediator complex, a co-activator involved in the regulated transcription of nearly all RNA polymerase II-dependent genes. Mediator functions as a bridge to convey information from gene-specific regulatory proteins to the basal RNA polymerase II transcription machinery (Xiaohui Liu et al. 2008)	It has been shown in prostate cancer that the loss of MED17 significantly decreases both androgen-dependent and -independent cellular proliferation, inhibits cell cycle progression, and increases apoptosis. Therefore, it appears to play a role in tumorigenesis at least in this tissue through transcriptional de-regulation (Vijayvargia et al. 2007)	Cell signaling/proliferation module in Figure 2A. General transcription pathway in Figure 3A.
NCOA3	nuclear receptor coactivator 3	Interacts with nuclear hormone receptors to enhance their transcriptional activator functions. The encoded protein has histone acetyltransferase activity and recruits p300/CBP-associated factor and CREB binding protein as part of a multisubunit co-activation complex.	Both tumorigenesis predisposing polymorphisms (Burwinkel et al. 2005) and somatic alterations –mostly in transcriptional level due to copy number changes (Henke et al. 2004)– have been observed in several cancer types.	Cell signaling/proliferation module in Figure 2A. General transcription pathway in Figure 3A.
PRKCD	Protein kinase C, delta	PKC (Protein kinase C) family members –family of serine- and threonine-specific protein kinases activated by calcium and diacylglycerol– phosphorylate a wide variety of protein targets and are known to be involved in diverse cellular signaling pathways (Durgan et al. 2007; Ren et al. 2002).	Its cellular location has been shown to play an important role in balancing between its proapoptotic and antiapoptotic functions and in the activation of downstream signaling pathways (Gomel et al. 2007). It is frequently lost –and coherently down-regulated– in squamous cell carcinomas (Yadav et al. 2010).	Cell signaling/proliferation module in Figure 2A. Cell cycle, Neurotrophin signaling, Chemokine signaling pathways in Figure 3A.
RHEB	Ras Homolog	Vital in regulation of	Through its involvement in the	Cell

	Enriched In Brain	growth and cell cycle progression due to its role in the insulin/TOR/S6K signaling pathway (Long et al. 2005; Tee et al. 2005).	TOR pathway, and via transcriptional de-regulation, it is known to participate in oncogenesis (Kobayashi et al. 2010).	signaling/proliferation module in Figure 2A. PI3K signaling, Protein synthesis pathways in Figure 3A.

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