

Supplementary Table 2 RAS mutation frequencies in human cancer									
Cancer	Samples	Alterations	KRAS	Alterations	NRAS	Alterations	HRAS	All RAS	Study; Refs
Pancreatic ductal adenocarcinoma	114	114	100.0	0	0.0	0	0.0	100.0	JHU; 1
Pancreatic ductal adenocarcinoma	99	94	84.5	0	0.0	0	0.0	94.9	ICGC; 2
Pancreatic ductal adenocarcinoma	3	3	100.0	0	0.0	0	0.0	100.0	TGen; 3
Total	216	211	97.7	0	0.0	0	0.0	97.7	
Colorectal adenocarcinoma	11	6	54.5	0	0.0	0	0.0	54.5	JHU; 4
Colorectal adenocarcinoma	11	5	45.5	2	18.2	0	0.0	63.6	Broad; 5
Colorectal adenocarcinoma	72	37	51.4	2	2.8	0	0.0	54.2	Genentech; 6
Colorectal adenocarcinoma	224	94*	42.0	20*	8.9	0	0.0	48.7	TCGA; 7
Total	318	142	44.7	24	7.5	0	0.0	52.2	
Multiple myeloma	67	17	25.4	17	25.4	0	0.0	50.7	CGP; 8
Multiple myeloma	205	45*	22.0	37*	18.0	0	0.0	39.0	Broad;9
Total	272	62	22.8	54	19.9	0	0.0	42.6	
Lung adenocarcinoma	57	13	22.8	1	1.8	0	0.0	24.6	Genentech; 10
Lung adenocarcinoma	163	60	36.8	3	1.8	0	0.0	38.7	TSP; 11
Lung adenocarcinoma	230	75	32.6	1	0.4	1	0.4	33.5	TCGA; in press
Lung adenocarcinoma	183	49	26.8	1	0.5	1	0.5	27.9	Broad; 12
Total	637	197	30.9	6	0.9	2	0.3	32.2	
Skin cutaneous melanoma	278	4	1.4	85	30.1	3	1.1	33.1	TCGA; provisional
Skin cutaneous melanoma	121	0	0.0	31	25.6	1	0.8	26.4	Broad; 13
Skin cutaneous melanoma	91	0	0.0	19	20.9	1	1.1	22.0	Yale; 14
Total	490	4	0.8	135	27.6	5	1.0	29.4	
Uterine corpus endometrioid carcinoma	248	53*	21.4	9*	3.6	1	0.4	24.6	TCGA; 15
Uterine carcinosarcoma	57	7	12.3	1	1.8	0	0.0	14.0	TCGA; provisional
Thyroid carcinoma	401	4	1.0	34	8.5	14	3.5	13.0	TCGA; provisional
Stomach adenocarcinoma	220	25	11.4	2	0.9	0	0.0	12.3	TCGA; provisional
Acute myeloid leukemia	200	8	4.0	15	7.5	0	0.0	11.5	TCGA; 16
Acute myeloid leukemia	55	0	0.0	2	3.6	4	7.3	10.9	ICGC (KR)
Total	255	8	3.1	17	6.7	4	1.6	11.4	
Bladder urothelial carcinoma	99	7	7.1	2	2.0	15	15.2	24.2	BGI; 17
Bladder urothelial carcinoma	130	0	0.0	2	1.5	6	4.6	6.2	TCGA; 18
Bladder urothelial carcinoma	97	4	4.1	0	0.0	0	0.0	4.1	MSKCC; 19
Bladder cancer	15	2	13.3	0	0.0	0	0.0	13.0	20
Bladder urothelial carcinoma	28	0	0.0	1	3.6	0	0.0	3.6	TCGA; provisional
Total	369	13	3.5	5	1.4	21	5.9	10.6	
Cervical adenocarcinoma	24	2	8.3	0	0.0	0	0.0	8.3	Broad;21
Head and neck squamous cell carcinoma	32	0	0.0	0	0.0	3	9.4	9.4	JHU; 22
Head and neck squamous cell carcinoma	74	1	1.4	0	0.0	4	5.4	6.8	Broad; 23
Head and neck squamous cell carcinoma	279	1	0.4	1	0.4	11	3.9	4.7	TCGA; in revision
Total	385	2	0.5	1	0.3	18	4.7	5.5	
Diffuse large B-cell lymphoma	58	3	0.0	0	0.0	0	0.0	5.2	Broad; 24
Gastric carcinoma	100	4	4.0	1	1.0	0	0.0	5.0	25
Esophageal adenocarcinoma	146	6	4.1	0	0.0	1	0.7	4.8	Broad; 26
Chronic lymphocytic leukaemia	160	3	1.9	4	2.5	0	0.0	4.4	Broad; 27

Lung squamous cell carcinoma	63	3	4.8	0	0.0	0	0.0	4.8	Genentech; 10
Lung squamous cell carcinoma	178	2	1.1	0	0.0	5	2.8	3.9	TCGA; 28
Total	226	5	2.2	0	0.0	5	2.2	4.4	
Small cell lung carcinoma	29	1	3.4	0	0.0	0	0.0	3.4	CLCGP; 29
Small cell lung carcinoma	42	0	0.0	0	0.0	1	2.4	2.4	JHU; 30
Total	71	1	1.4	0	0.0	1	1.4	2.8	
Renal papillary cell carcinoma	168	2	1.2	1	0.6	1	0.6	2.4	TCGA; provisional
Adenoid cystic carcinoma	60	0	0.0	0	0.0	1	1.7	1.7	MSKCC; 31
Medulloblastoma & pilocytic astrocytoma	193	2	1.0	1	0.5	0	0.0	1.6	ICGC (DE)
Chromophobe renal cell carcinoma	66	0	0.0	1	1.5	0	0.0	1.5	TCGA; provisional
Hepatocellular carcinoma	231	2	0.9	1	0.4	0	0.0	1.3	AMC; 32
Hepatocellular carcinoma	27	0	0.0	0	0.0	0	0.0	0.0	RIKEN; 33
Hepatocellular carcinoma	88	0	0.0	2	2.3	0	0.0	2.3	34
Total	346	2	0.6	3	0.9	0	0.0	1.4	
Breast invasive carcinoma (TNBC)	65	0	0.0	2	3.1	0	0.0	3.1	BC; 35
Breast invasive carcinoma (79 ER+/21 ER-)	100	1	1.0	0	0.0	1	1.0	2.0	Sanger; 36
Breast cancer (primary, all major subtypes)	103	0	0.0	0	0.0	0	0.0	0.0	Broad; 37
Breast triple negative/lobular cancer	117	4	3.4	3	2.6	3	2.6	7.7	ICGC (UK)
Breast invasive carcinoma	825	3	3.6	0	0.0	0	0.0	3.6	TCGA; 38
Total	1,210	8	0.7	5	0.4	4	0.3	1.4	
Ovarian serous adenocarcinoma	316	2	0.6	2	0.6	0	0.0	1.3	TCGA; 39
Cervical squamous cell carcinoma	79	1	1.3	0	0.0	0	0.0	1.3	Broad; 21
Adrenocortical carcinoma	91	0	0.0	1	1.1	0	0.0	1.1	TCGA; provisional
Prostate adenocarcinoma	61	1	1.6	0	0.0	0	0.0	1.6	Michigan; 40
Prostate adenocarcinoma	103	1	1.0	0	0.0	0	0.0	1.0	MSKCC; 41
Prostate adenocarcinoma	112	0	0.0	0	0.0	1	0.9	0.9	Broad/Cornell; 42
Prostate adenocarcinoma	57	0	0.0	0	0.0	0	0.0	0.0	Broad/Cornell; 43
Prostate adenocarcinoma	261	0	0.0	0	0.0	2	0.8	0.8	TCGA; provisional
Total	594	2	0.3	0	0.0	3	0.5	0.8	
Neuroblastoma	240	0	0.0	2	0.8	0	0.0	0.8	Broad/GSC; 44
Glioblastoma multiforme	291	2	0.7	0	0.0	0	0.0	0.7	TCGA; 45
Brain lower grade glioma	289	1	0.3	1	0.3	0	0.0	0.7	TCGA; provisional
Medulloblastoma	125	0	0.0	1	0.8	0	0.0	0.8	ICGC; 46
Medulloblastoma	37	0	0.0	0	0.0	0	0.0	0.0	PCGP; 47
Medulloblastoma	92	0	0.0	0	0.0	0	0.0	0.0	Broad; 48
Total	254	0	0.0	1	0.8	0	0.0	0.4	
Renal clear cell carcinoma	14	0	0.0	0	0.0	0	0.0	0.0	CGP; 49
Renal clear cell carcinoma	98	0	0.0	0	0.0	0	0.0	0.0	BGI; 50
Renal clear cell carcinoma	424	1	0.2	0	0.0	1	0.2	0.4	TCGA; 51
Total	536	1	0.2	0	0.0	1	0.2	0.4	
Esophageal adenocarcinoma	11	0	0.0	0	0.0	0	0.0	0.0	JHU; 52
Esophageal squamous cell carcinoma	12	0	0.0	0	0.0	0	0.0	0.0	JHU; 52
Esophageal squamous cell carcinoma	158	0	0.0	0	0.0	0	0.0	0.0	53
Esophageal squamous cell carcinoma	139	0	0.0	0	0.0	0	0.0	0.0	54

Total	309	0	0.0	0	0.0	0	0.0	0.0	0.0
Osteosarcoma (paediatric)	20	0	0.0	0	0.0	0	0.0	0.0	55
Ovarian small cell carcinoma	12	0	0.0	0	0.0	0	0.0	0.0	TGen; 56
Ovarian small cell carcinoma	2	0	0.0	0	0.0	0	0.0	0.0	McGill; 57
Ovarian small cell carcinoma	12	0	0.0	0	0.0	0	0.0	0.0	MSKCC; 58
Total	26	0	0.0	0	0.0	0	0.0	0.0	
Rhabdoid tumors	35	0	0.0	0	0.0	0	0.0	0.0	Broad; 59
Sarcoma	207	0	0.0	0	0.0	0	0.0	0.0	MSKCC/Broad; 60
Small intestine neuroendocrine tumors	55	0	0.0	0	0.0	0	0.0	0.0	Broad; 61
T-cell prolymphocytic leukemia	40	0	0.0	0	0.0	0	0.0	0.0	62

AMC, Asan Medical Center; BC, British Columbia; BGI, Beijing Genomics Institute, Broad, <http://cancergenome.broadinstitute.org>; CGP, Cancer Genomics Project (Tokyo); CLCGP; Clinical Lung Cancer Genome Project; GSC, Genome Sciences Centre (BC Cancer Agency); ICGC, International Cancer Genome Consortium (AU, Australia; CA, Canada; DE, Germany; KR, South Korea; UK, United Kingdom); JHU; Johns Hopkins University; METABRIC, Molecular Taxonomy of Breast Cancer International Consortium; MSKCC; Memorial Sloan Kettering Cancer Center; PCGP, Pediatric Cancer Genome Project; TCGA, The Cancer Genome Atlas, <https://tcga-data.nci.nih.gov/tcga/>; TSP, Tumor Sequencing Project; *Some KRAS and NRAS mutations were found in the same patients. Data were also compiled from <http://www.cbioportal.org/public-portal/>

References

- Jones, S. et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. *Science* **321**, 1801-6 (2008).
- Biankin, A.V. et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. *Nature* **491**, 399-405 (2012).
- Liang, W.S. et al. Genome-wide characterization of pancreatic adenocarcinoma patients using next generation sequencing. *PLoS one* **7**, e43192 (2012).
- Wood, L.D. et al. The genomic landscapes of human breast and colorectal cancers. *Science* **318**, 1108-13 (2007).
- Bass, A.J. et al. Genomic sequencing of colorectal adenocarcinomas identifies a recurrent VTI1A-TCF7L2 fusion. *Nat Genet* **43**, 964-8 (2011).
- Seshagiri, S. et al. Recurrent R-spondin fusions in colon cancer. *Nature* **488**, 660-4 (2012).
- Comprehensive molecular characterization of human colon and rectal cancer. *Nature* **487**, 330-7 (2012).
- Bolli, N. et al. Heterogeneity of genomic evolution and mutational profiles in multiple myeloma. *Nat Commun* **5**, 2997 (2014).
- Lohr, J.G. et al. Widespread genetic heterogeneity in multiple myeloma: implications for targeted therapy. *Cancer Cell* **25**, 91-101 (2014).
- Kan, Z. et al. Diverse somatic mutation patterns and pathway alterations in human cancers. *Nature* **466**, 869-73 (2010).
- Ding, L. et al. Somatic mutations affect key pathways in lung adenocarcinoma. *Nature* **455**, 1069-75 (2008).
- Imielinski, M. et al. Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing. *Cell* **150**, 1107-20 (2012).
- Hodis, E. et al. A landscape of driver mutations in melanoma. *Cell* **150**, 251-63 (2012).
- Krauthammer, M. et al. Exome sequencing identifies recurrent somatic RAC1 mutations in melanoma. *Nat Genet* **44**, 1006-14 (2012).
- Kandoth, C. et al. Integrated genomic characterization of endometrial carcinoma. *Nature* **497**, 67-73 (2013).
- Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. *New Engl J Med* **368**, 2059-74 (2013).
- Guo, G. et al. Whole-genome and whole-exome sequencing of bladder cancer identifies frequent alterations in genes involved in sister chromatid cohesion and segregation. *Nat Genet* **45**, 1459-63 (2013).
- Comprehensive molecular characterization of urothelial bladder carcinoma. *Nature* (2014).

19. Iyer, G. et al. Prevalence and co-occurrence of actionable genomic alterations in high-grade bladder cancer. *J Clin Oncol* **31**, 3133-40 (2013).
20. Cazier, J.B. et al. Whole-genome sequencing of bladder cancers reveals somatic CDKN1A mutations and clinicopathological associations with mutation burden. *Nat Commun* **5**, 3756 (2014).
21. Ojesina, A.I. et al. Landscape of genomic alterations in cervical carcinomas. *Nature* **506**, 371-5 (2014).
22. Agrawal, N. et al. Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1. *Science* **333**, 1154-7 (2011).
23. Stransky, N. et al. The mutational landscape of head and neck squamous cell carcinoma. *Science* **333**, 1157-60 (2011).
24. Lohr, J.G. et al. Discovery and prioritization of somatic mutations in diffuse large B-cell lymphoma (DLBCL) by whole-exome sequencing. *Proc Natl Acad Sci USA* **109**, 3879-84 (2012).
25. Wang, K. et al. Whole-genome sequencing and comprehensive molecular profiling identify new driver mutations in gastric cancer. *Nat Genet* **46**, 573-82 (2014).
26. Dulak, A.M. et al. Exome and whole-genome sequencing of esophageal adenocarcinoma identifies recurrent driver events and mutational complexity. *Nat Genet* **45**, 478-86 (2013).
27. Landau, D.A. et al. Evolution and impact of subclonal mutations in chronic lymphocytic leukemia. *Cell* **152**, 714-26 (2013).
28. Comprehensive genomic characterization of squamous cell lung cancers. *Nature* **489**, 519-25 (2012).
29. Peifer, M. et al. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. *Nat Genet* **44**, 1104-10 (2012).
30. Rudin, C.M. et al. Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer. *Nat Genet* **44**, 1111-6 (2012).
31. Ho, A.S. et al. The mutational landscape of adenoid cystic carcinoma. *Nat Genetics* **45**, 791-8 (2013).
32. Ahn, S.M. et al. A genomic portrait of resectable hepatocellular carcinomas: Implications of RB1 and FGF19 aberrations for patient stratification. *Hepatology* (2014).
33. Fujimoto, A. et al. Whole-genome sequencing of liver cancers identifies etiological influences on mutation patterns and recurrent mutations in chromatin regulators. *Nat Genet* **44**, 760-4 (2012).
34. Cleary, S.P. et al. Identification of driver genes in hepatocellular carcinoma by exome sequencing. *Hepatology* **58**, 1693-702 (2013).
35. Shah, S.P. et al. The clonal and mutational evolution spectrum of primary triple-negative breast cancers. *Nature* **486**, 395-9 (2012).
36. Stephens, P.J. et al. The landscape of cancer genes and mutational processes in breast cancer. *Nature* **486**, 400-4 (2012).
37. Banerji, S. et al. Sequence analysis of mutations and translocations across breast cancer subtypes. *Nature* **486**, 405-9 (2012).
38. Comprehensive molecular portraits of human breast tumours. *Nature* **490**, 61-70 (2012).
39. Integrated genomic analyses of ovarian carcinoma. *Nature* **474**, 609-15 (2011).
40. Grasso, C.S. et al. The mutational landscape of lethal castration-resistant prostate cancer. *Nature* **487**, 239-43 (2012).
41. Taylor, B.S. et al. Integrative genomic profiling of human prostate cancer. *Cancer Cell* **18**, 11-22 (2010).
42. Barbieri, C.E. et al. Exome sequencing identifies recurrent SPOP, FOXA1 and MED12 mutations in prostate cancer. *Nat Genetics* **44**, 685-9 (2012).
43. Baca, S.C. et al. Punctuated evolution of prostate cancer genomes. *Cell* **153**, 666-77 (2013).
44. Pugh, T.J. et al. The genetic landscape of high-risk neuroblastoma. *Nat Genet* **45**, 279-84 (2013).
45. Brennan, C.W. et al. The somatic genomic landscape of glioblastoma. *Cell* **155**, 462-77 (2013).
46. Jones, D.T. et al. Dissecting the genomic complexity underlying medulloblastoma. *Nature* **488**, 100-5 (2012).

47. Robinson, G. et al. Novel mutations target distinct subgroups of medulloblastoma. *Nature* **488**, 43-8 (2012).
48. Pugh, T.J. et al. Medulloblastoma exome sequencing uncovers subtype-specific somatic mutations. *Nature* **488**, 106-10 (2012).
49. Sato, Y. et al. Integrated molecular analysis of clear-cell renal cell carcinoma. *Nat Genet* **45**, 860-7 (2013).
50. Guo, G. et al. Frequent mutations of genes encoding ubiquitin-mediated proteolysis pathway components in clear cell renal cell carcinoma. *Nat Genet* **44**, 17-9 (2012).
51. Comprehensive molecular characterization of clear cell renal cell carcinoma. *Nature* **499**, 43-9 (2013).
52. Agrawal, N. et al. Comparative genomic analysis of esophageal adenocarcinoma and squamous cell carcinoma. *Cancer Discov* **2**, 899-905 (2012).
53. Song, Y. et al. Identification of genomic alterations in oesophageal squamous cell cancer. *Nature* **509**, 91-5 (2014).
54. Lin, D.C. et al. Genomic and molecular characterization of esophageal squamous cell carcinoma. *Nat Genet* **46**, 467-73 (2014).
55. Chen, X. et al. Recurrent somatic structural variations contribute to tumorigenesis in pediatric osteosarcoma. *Cell Rep* **7**, 104-12 (2014).
56. Ramos, P. et al. Small cell carcinoma of the ovary, hypercalcemic type, displays frequent inactivating germline and somatic mutations in SMARCA4. *Nat Genet* **46**, 427-9 (2014).
57. Witkowski, L. et al. Germline and somatic SMARCA4 mutations characterize small cell carcinoma of the ovary, hypercalcemic type. *Nat Genet* **46**, 438-43 (2014).
58. Jelinic, P. et al. Recurrent SMARCA4 mutations in small cell carcinoma of the ovary. *Nat Genet* **46**, 424-6 (2014).
59. Lee, R.S. et al. A remarkably simple genome underlies highly malignant pediatric rhabdoid cancers. *J Clin Invest* **122**, 2983-8 (2012).
60. Barretina, J. et al. Subtype-specific genomic alterations define new targets for soft-tissue sarcoma therapy. *Nat Genet* **42**, 715-21 (2010).
61. Francis, J.M. et al. Somatic mutation of CDKN1B in small intestine neuroendocrine tumors. *Nat Genet* **45**, 1483-6 (2013).
62. Kiel, M.J. et al. Integrated genomic sequencing reveals mutational landscape of T-cell prolymphocytic leukemia. *Blood* (2014).