

## Supplementary Data

**Table S1. Mutation signature gene lists**

S1.1 KRAS signature75 genes		
ID	Gene Name	Description
AK022594	AK022594	Homo sapiens cDNA FLJ12532 fis, clone NT2RM4000200
AK130878	AK130878	Homo sapiens cDNA FLJ27368 fis, clone UBA03195
NM_001164	APBB1	Amyloid beta (A4) precursor protein-binding, family B, member 1 (Fe65)
NM_024590	ARSJ	Arylsulfatase family, member J
NM_015338	ASXL1	Additional sex combs like 1
NM_001677	ATP1B1	ATPase, Na <sup>+</sup> /K <sup>+</sup> transporting, beta 1 polypeptide
BC030102	BC030102	cDNA clone IMAGE:4796690
NM_030766	BCL2L14	BCL2-like 14 (apoptosis facilitator)
NM_001202	BMP4	Bone morphogenetic protein 4
BX647159	BX647159	DKFZp686H14196 (from clone DKFZp686H14196)
NM_013399	C16orf5	Cell death inducing protein
NM_016470	C20orf111	Chromosome 20 open reading frame 111
NM_00108047 2	C20orf142	Fat storage-inducing transmembrane protein 2 (FITM2)
NM_015511	C20orf4	Chromosome 20 open reading frame 4
NM_001218	CA12	Carbonic anhydrase XII
NM_000719	CACNA1C	Calcium channel, voltage-dependent, L type, alpha 1C subunit
NM_032587	CARD6	Caspase recruitment domain family, member 6
AK098629	CNNM3	Cyclin M3
NM_000784	CYP27A1	Cytochrome P450, family 27, subfamily A, polypeptide 1
AL390175	DKFZp547 K054	ZNF853 zinc finger protein 853
NM_012242	DKK1	Dickkopf homolog 1 (Xenopus laevis)
NM_001946	DUSP6	Dual specificity phosphatase 6 (DUSP6)
NM_207032	EDN3	Endothelin 3 (EDN3),
NM_006208	ENPP1	Ectonucleotidepyrophosphatase/phosphodiesterase 1
NM_021727	FADS3	Fatty acid desaturase 3
NM_015566	FAM169A	Family with sequence similarity 169, member A
NM_015101	GLT25D2	Glycosyltransferase 25 domain containing 2
ENST0000037 1081	GNAS	Guanine nucleotide-binding protein G(s) subunit alpha isoforms
NM_00103000 4	HNF4A	Hepatocyte nuclear factor 4, alpha
NM_002147	HOXB5	Homeobox B5
NM_018952	HOXB6	Homeobox B6
NM_024016	HOXB8	Homeobox B8
NM_033439	IL33	Interleukin 33
NM_018689	KIAA1199	KIAA1199
NM_002776	KLK10	Kallikrein-relatedpeptidase 10
NM_144947	KLK11	Kallikrein-relatedpeptidase 11
NM_019079	L1TD1	LINE-1 type transposase domain containing 1
NM_00100155	LEMD1	LEM domain containing 1

2		
XM_00171520 2	LOC10013 0910	hypothetical protein LOC100130910
ENST0000039 8035	LOC12037 6	hypothetical protein LOC120376
NM_000239	LYZ	Lysozyme (renal amyloidosis)
NM_000260	MYO7A	Myosin VIIA
THC2669157	OIT3	Oncoprotein induced transcript 3
NM_007350	PHLDA1	Pleckstrin homology-like domain, family A, member 1
NM_080476	PIGU	Phosphatidylinositol glycan anchor biosynthesis, class U
NM_032562	PLA2G12B	Phospholipase A2, group XIIB
NM_002657	PLAGL2	Pleiomorphic adenoma gene-like 2
NM_172236	POFUT1	Protein O-fucosyltransferase 1
NM_080685	PTPN13	Protein tyrosine phosphatase, non-receptor type 13 (APO-1/CD95 (Fas)-associated phosphatase)
NM_007238	PXMP4	Peroxisomal membrane protein 4
NM_014899	RHOBTB3	Rho-related BTB domain containing 3
NM_198232	RNASE1	Ribonuclease, RNase A family, 1 (pancreatic)
NM_153225	RPESP	RPE-spondin (RPESP)
NM_005980	S100P	S100 calcium binding protein P
NM_002639	SERPINB5	Serpin peptidase inhibitor, clade B (ovalbumin), member 5
NM_003059	SLC22A4	Solute carrier family 22 (organic cation/ergothioneine transporter), member 4
NM_000112	SLC26A2	Solute carrier family 26 (sulfate transporter), member 2
NM_021095	SLC5A6	Solute carrier family 5 (sodium-dependent vitamin transporter), member 6
NM_014331	SLC7A11	Solute carrier family 7, (cationic amino acid transporter, y+ system) member 11
NM_019844	SLCO1B3	Solute carrier organic anion transporter family, member 1B3
NM_032229	SLITRK6	SLIT and NTRK-like family, member 6
NM_003098	SNTA1	Syntrophin, alpha 1 (dystrophin-associated protein A1, 59kDa, acidic component)
NM_00104263 3	SNX21	Sorting nexin family member 21
NM_00103495 4	SORBS1	Sorbin and SH3 domain containing 1
NM_145263	SPATA18	Spermatogenesis associated 18 homolog (rat)
NM_006804	STARD3	StAR-related lipid transfer
THC2624002	THC26240 02	HUMAN (Q9BXR7) Interleukin 10 (Fragment)
THC2634713	THC26347 13	Unknown
THC2699065	THC26990 65	DTDP-glucose 4,6-dehydratase (Fragment), partial (9%)
THC2708669	THC27086 69	Dihydropteroate synthase (DHPS) (Dihydropteroatepyrophosphorylase) , partial (5%)
NM_138554	TLR4	Toll-like receptor 4
NM_144649	TMEM71	Transmembrane protein 71
BE893137	TNIK	TRAF2 and NCK interacting kinase
NM_032865	TNS4	Tensin 4
NM_021202	TP53INP2	Tumor protein p53 inducible nuclear protein 2

<b>S1.2 BRAFsignature 58 genes</b>		
<b>ID</b>	<b>Gene Name</b>	<b>Description</b>
NM_001009185	ACSL6	Acyl-CoA synthetase long-chain family member 6
NM_006408	AGR2	Anterior gradient homolog 2 (Xenopus laevis)
NM_001621	AHR	Aryl hydrocarbon receptor
NM_001018060	AIFM3	Apoptosis-inducing factor, mitochondrion-associated, 3
NM_007193	ANXA10	Annexin A10
NM_005224	ARID3A	AT rich interactive domain 3A
NM_005170	ASCL2	Achaete-scute complex homolog 2 (Drosophila)
NM_015338	ASXL1	Additional sex combs like 1 (Drosophila)
NM_004655	AXIN2	Axin 2 (conductin, axil)
BX427767	BX427767	cDNA clone CS0DM012YK01 3-PRIME
BX647159	BX647159	cDNA DKFZp686H14196
NM_153256	C10orf47	Chromosome 10 open reading frame 47
NM_018363	C10orf59	RNLS renalase, FAD-dependent amine oxidase
NM_025113	C13orf18	Chromosome 13 open reading frame 18
BC029662	C20orf142	Fat storage-inducing transmembrane protein 2 (FITM2)
NM_004364	CEBPA	CCAAT/enhancer binding protein
NM_015147	CEP68	Centrosomal protein 68kDa
CR616309	CR616309	LIMF1-lipase maturation factor 1
NM_033081	DIDO1	Death inducer-obliterator 1
XM_085578	DNAH2	Dynein, axonemal, heavy chain 2
NM_152511	DUSP18	Dual specificity phosphatase 18 (DUSP18), mRNA [NM_152511]
NM_017549	EPDR1	Ependyminrelatedprotein 1 (zebrafish)
NM_004454	ETV5	Ets variant gene 5 (ets-related molecule)
NM_178026	GGT7	Gamma-glutamyltransferase 7
NM_000273	GPR143	G protein-coupled receptor 143
NM_024501	HOXD1	Homeobox D1
THC2657554	KCNK5	Potassium channel, subfamily K, member 5
AK025743	LOC157860	hypotheticalprotein LOC157860
NM_001013642	LOC388610	hypothetical LOC388610
NM_000249	MLH1	MutL homolog 1, colon cancer, nonpolyposis type 2 (E. coli)
NM_014484	MOCS3	Molybdenum cofactor synthesis 3
NM_024657	MORC4	MORC family CW-type zinc finger 4
NM_033100	PCDH21	Protocadherin 21
NM_002657	PLAGL2	Pleiomorphic adenoma gene-like 2 (PLAGL2), mRNA [NM_002657]
NM_015352	POFUT1	Protein O-fucosyltransferase 1
NM_012094	PRDX5	Peroxiredoxin 5
NM_030667	PTPRO	Protein tyrosine phosphatase, receptor type, O
NM_014298	QPRT	Quinolatephosphoribosyltransferase (nicotinate-nucleotide pyrophosphorylase (carboxylating))
NM_004163	RAB27B	RAB27B, member RAS oncogene family
NM_006834	RAB32	RAB32, member RAS oncogene family 32

NM_032044	REG4	Regenerating islet-derived family, member 4
NM_017763	RNF43	Ring finger protein 43
NM_001649	SHROOM2	shroom family member 2
NM_020717	SHROOM4	Shroom family member 4
NM_173596	SLC39A5	Solute carrier family 39 (metal ion transporter), member 5
NM_014331	SLC7A11	Solute carrier family 7, (cationic amino acid transporter, y+ system) member 11
NM_019008	SMCR7L	Smith-Magenis syndrome chromosome region, candidate 7-like
NR_003239	SNHG11	Small nucleolar RNA host gene (non-protein coding) 11
NM_014587	SOX8	SRY (sex determining region Y)-box 8
NM_003122	SPINK1	Serine peptidase inhibitor, Kazal type 1
NM_005423	TFF2	Trefoil factor 2 (spasmolytic protein 1)
NM_003279	TNNC2	Troponin C type 2 (fast)
BC107798	TNNT1	Troponin T type 1 (skeletal, slow)
NM_203297	TRIM7	Tripartite motif-containing 7
NM_023076	UNKL	unkempt homolog (Drosophila)-like
NM_006113	VAV3	Vav 3 guanine nucleotide exchange factor
NM_033132	ZIC5	Zic family member 5 (odd-paired homolog, Drosophila)
NM_080752	ZSWIM3	Zinc finger, SWIM-type containing 3

<b>S1.3 PIK3CA signature 49 genes</b>		
<b>ID</b>	<b>Name</b>	<b>Description</b>
NM_015338	ASXL1	Additional sex combs like 1 (Drosophila) (ASXL1)
NM_001677	ATP1B1	ATPase, Na <sup>+</sup> /K <sup>+</sup> transporting, beta 1 polypeptide
THC2708669	AQP5	Aquaporin 5
NM_001677	ATP1B1	ATPase, Na <sup>+</sup> /K <sup>+</sup> transporting, beta 1 polypeptide
NM_016470	C20orf111	Chromosome 20 open reading frame 111
NM_001080472	C20orf142	Fat storage-inducing transmembrane protein 2 (FITM2)
NM_015511	C20orf4	Chromosome 20 open reading frame 4
NM_080748	C20orf52	ROMO1 - reactive oxygen species modulator 1
NM_004929	CALB1	Calbindin 1
NM_030877	CTNBL1	Catenin, beta like 1
NM_000784	CYP27A1	Cytochrome P450, family 27, subfamily A, polypeptide 1
NM_033081	DIDO1	Death inducer-obliterator 1
NM_052951	DNTTIP1	deoxynucleotidyltransferase, terminal, interacting protein 1
NM_001946	DUSP6	Dual specificity phosphatase 6
NM_014183	DYNLRB1	Dynein, light chain, roadblock-type 1
NM_002212	EIF6	Eukaryotic translation initiation factor 6
CR936791	FAM169A	Family with sequence similarity 169, member A
NM_001452	FOXF2	Forkhead box F2
NM_001098722	GNG4	Guanine nucleotide binding protein (G protein), gamma 4
NM_000273	GPR143	G protein-coupled receptor 143
NM_014278	HSPA4L	Heat shock 70kDa protein 4-like
NM_021258	IL22RA1	Interleukin 22 receptor, alpha 1
NM_003740	KCNK5	Potassium channel, subfamily K, member 5

NM_198991	KCTD1	Potassium channel tetramerisation domain containing 1
NM_018689	KIAA1199	KIAA1199 , colon cancer secreted protein 1
NM_002776	KLK10	Kallikrein-relatedpeptidase 10
NM_144947	KLK11	Kallikrein-relatedpeptidase 11
THC2688670	LOC646951	similar to hCG1786685
THC2669157	OIT3	Oncoprotein induced transcript 3
NM_032562	PLA2G12B	Phospholipase A2, group XIIB
NM_002657	PLAGL2	Pleiomorphic adenoma gene-like 2
NM_025225	PNPLA3	Patatin-like phospholipase domain containing 3
NM_015352	POFUT1	Protein O-fucosyltransferase 1
NM_004163	RAB27B	RAB27B, member RAS oncogene family
NM_198232	RNASE1	Ribonuclease, RNase A family, 1
NM_153225	RPESP	RPE-spondin
NM_002639	SERPINB5	Serpin peptidase inhibitor, clade B (ovalbumin), member 5
NM_019844	SLCO1B3	Solute carrier organic anion transporter family, member 1B3 (SLCO1B3), mRNA [NM_019844]
NR_003239	SNHG11	Small nucleolar RNA host gene (non-protein coding) 11
NM_001034954	SORBS1	Sorbin and SH3 domain containing 1 (SORBS1)
NM_145263	SPATA18	Spermatogenesis associated 18 homolog (rat)
NM_001062	TCN1	Transcobalamin I (vitamin B12 binding protein, R binder family)
NM_022748	TNS3	Tensin 3
NM_033342	TRIM7	Tripartite motif-containing 7
NM_130783	TSPAN18	Tetraspanin 18 (TSPAN18)
Unknown	Unknown	Unknown
NM_021197	WFDC1	WAP four-disulfide core domain 1
NM_013313	YPEL1	Yippee-like 1 (drosophila)
NM_080752	ZSWIM3	Zinc finger, SWIM-type containing 3

**Table S2. Enriched molecular and cellular functions of the KRAS, BRAF and PIK3CA mutation signatures.** The enriched biological functions were analyzed using Ingenuity Pathways Analysis ([www.ingenuity.com](http://www.ingenuity.com)).

<b>KRAS signature</b>		
<b>Name</b>	<b>p-value</b>	<b>Number of genes</b>
Cellular Movement	1.04E-05 - 4.47E-02	8
Cellular Development	6.23E-05 - 4.78E-02	15
Gene Expression	4.61E-04 - 3.84E-02	6
Cell Morphology	7.94E-04 - 4.47E-02	8
Lipid Metabolism	1.07E-03 - 4.78E-02	10
<b>PIK3CA signature</b>		
<b>Name</b>	<b>p-value</b>	<b>Number of genes</b>
Cell Cycle	2.40E-03 - 1.67E-02	2
Cell Death	2.40E-03 - 4.69E-02	4
Cell Morphology	2.40E-03 - 3.07E-02	2
Cell-To-Cell Signaling and Interaction	2.40E-03 - 4.92E-02	3
Cellular Assembly and Organization	2.40E-03 - 3.77E-02	2
<b>BRAF signature</b>		
<b>Name</b>	<b>p-value</b>	<b>Number of genes</b>
Cell Cycle	8.03E-05 - 4.83E-02	10
Gene Expression	4.37E-04 - 4.78E-02	5
Cellular Development	2.47E-03 - 4.51E-02	9
Cellular Growth and Proliferation	2.47E-03 - 4.23E-02	13
Carbohydrate Metabolism	2.88E-03 - 1.15E-02	2

**Table S3. Overlapping genes between EGFR-associated mutation gene signatures**

<i>KRAS</i>	<b>75</b>		
<i>PIKC3A</i>	21	<b>49</b>	
<i>BRAF</i>	6	11	<b>58</b>
	<i>KRAS</i>	<i>PIKC3A</i>	<i>BRAF</i>

**Table S4. Concordance analysis of AUC of specific mutation signatures with mutation status.** AUC was calculated from all 381 samples included. p-values refer to binomial exact test. Kappa= kappa statistics

<b>AUC (n=381)</b>	<b><i>KRAS</i> mutation</b>	<b><i>BRAF</i> mutation</b>	<b><i>PIK3CA</i> mutation</b>
<b><i>KRAS</i> signature</b>	0.77(p<0.0001) Kappa = 0.324	0.76 (p <0.0001) Kappa = 0.124	0.72 (p <0.0001) Kappa = 0.086
<b><i>BRAF</i> signature</b>	0.60 (p=0.0003) Kappa = -0.096	0.94 (p <0.0001) Kappa = 0.585	0.65 (p= 0.0002) Kappa = 0.141
<b><i>PIK3CA</i> signature</b>	0.66 (p<0.0001) Kappa = 0.236	0.87 (p<0.0001) Kappa =0.259	0.76 (p <0.0001) Kappa = 0.176