Mutations in the RAS-BRAF-MAPK-ERK pathway define a specific subgroup of patients with adverse clinical features and provide new therapeutic options in chronic lymphocytic leukemia

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Supplemental data

METHODS

Primary CLL cells

Cells were isolated from peripheral blood (PB) samples by Ficoll-Paque sedimentation (GE-Healthcare, Chicago, IL, USA). Thawed cells were cultured in fresh RPMI-1640 supplemented with 10% fetal bovine serum (FBS) (Life technologies; Carlsbad, CA, USA), 2 mM glutamine and 50 µg/mL penicillin-streptomycin (Life technologies) and cultured in a humidified atmosphere at 37ºC containing 5% carbon dioxide

Gene expression analysis

Gene expression profile (GEP) of 143 purified U-IGHV CLL samples from the CLL-ICGC project[8] was analyzed. Cases with mutations in the RAS-BRAF-MAPK-ERK pathway versus those without mutations were compared using the gene set enrichment analysis (GSEA) package version 2.0. The enrichment of the MAPK gene signature was investigated using the C2 Biocarta and C2 KEGG collection version 6,1 with a two-class analysis, 1000 permutations of gene sets and weighted metrics. Gene sets with a $p \leq 0.05$ and a false discovery rate (FDR) q-value≤10% and a normalized enrichment score (NES) ≥1.5 were considered to be significantly enriched in the *RAS-BRAF-MAPK-ERK* mutated group. Sequencing, expression and genotyping array data have been deposited at the European Genome-Phenome Archive (EGA, http://www.ebi.ac.uk/ega/), which is hosted at the European Bioinformatics Institute (EBI), under accession number EGAS00000000092.

Western blot analysis

Whole-cell protein extracts were obtained by lysing primary CLL cells and peripheral blood mononuclear cells (PBMC) obtained from healthy donors (online with Triton buffer (20 mM Tris-HCL pH 7.6, 150 mM NaCl, 1 mM EDTA, and 1% Triton X-100) supplemented with protease and phosphatase inhibitors [10 µg/mL leupeptin, 10 µg/mL aprotinin, 1 mM PMSF (phenylmethanesulfonyl fluoride), 2 mM PHIC I (sodium pyrophosphate decahydrate), PHIC II (β-glycerol phosphate disodium salt

pentahydrate), and 1 mM sodium orthovanadate (Sigma, Saint Louis, MO, USA)]. Proteins were quantified using Bio-Rad Protein Assay (Bio-Rad, Portland, ME, USA), separated in 12% SDS-PAGE and transferred to an Immobilon-P membrane (EMD Millipore, Billerica, MA, USA). Membranes were blocked with 2.5% phosphoBlocker Blocking Reagent (Cell Biolabs, San Diego, CA, USA) in Tris-Buffered Saline (TBS)-Tween 20, and probed with antibodies against phosphorylated- T202/Y204 ERK 1/2 and total ERK (Santa Cruz Biotechnology, Santa Cruz, CA, USA). Antibody binding was detected using secondary peroxidase-labeled anti-mouse and anti-rabbit antibodies (Sigma) and chemiluminescence was detected using a mini-LAS4000 Fujifilm device (Fujifilm. Tokyo, Japan). Equal protein loading was confirmed by probing membranes with α-tubulin antibody (Sigma).

Analysis of viability

Primary CLL cells were incubated for 24 or 48 hours with the indicated doses of the drugs and then stained with Annexin-V-Fluorescein isothiocyanate (FITC) and Propidium iodide (PI) (Ebiosciences, San Diego, CA, USA). Labeled samples were analyzed on an Attune focusing acoustic cytometer (Life Technologies). Viability (mean ± SEM) was calculated as the percentage of Annexin-V and PI negative cells in treated samples relative to the untreated ones.

BCR stimulation and quantification of p-ERK by flow cytometry

Primary CLL cells were starved for 1.5 hours in FBS-free RPMI ($5x10^6$ cells/mL) and preincubated with different doses of the drugs. Then, cells were stimulated for 2 minutes at 37°C with 10 μg/mL of anti-IgM (Southern Biotech, Birmingham, AL, USA) and 3.3 mM of hydrogen peroxide (Sigma), fixed for 1 hour with paraformaldehyde 2% and permeabilized by adding 70% ethanol overnight at −20°C. Intracellular unspecific staining was blocked with 10% mouse serum. Finally, cells were stained for phospho (T202 and Y204)-ERK1/2-phycoerythrin (PE) (Becton Dickinson, Franklin Lakes, NJ, USA) and 10000 cells were analyzed in an Attune acoustic cytometer (Life

Technologies). Median fluorescence intensity (MFI) of the unstained sample was subtracted to respective p-ERK stained sample.

Statistical analysis

Time to first treatment (TTFT) was calculated from the date of sampling to the first treatment or last follow-up. Overall survival (OS) was calculated from the date of sampling to the date of death or last follow-up. All statistical tests were two-sided with a p-value of 0.05 to be considered significant. All the analyses were conducted using SPSS 20 (www.ibm.com) software.

Figure S1

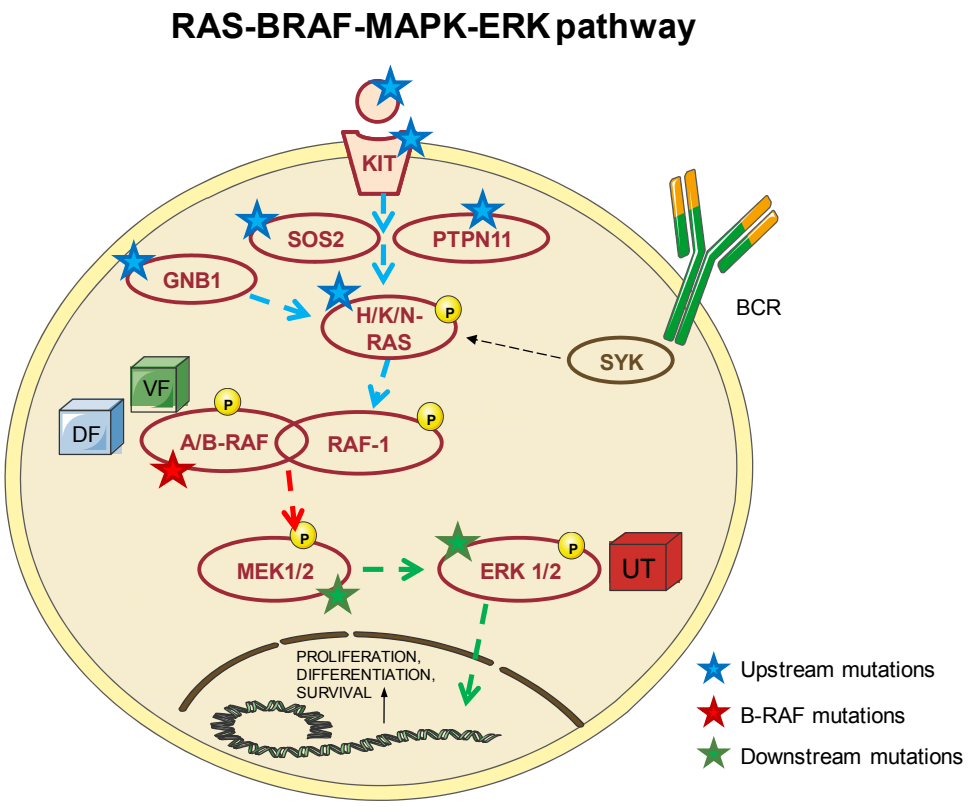

Figure S1. Scheme of the MAPK pathway with stars indicating the genes with mutations found in our cohort (detailed in Table 1). VF: vemurafenib, DF: dabrafenib, UT: Ulixertinib

Figure S2

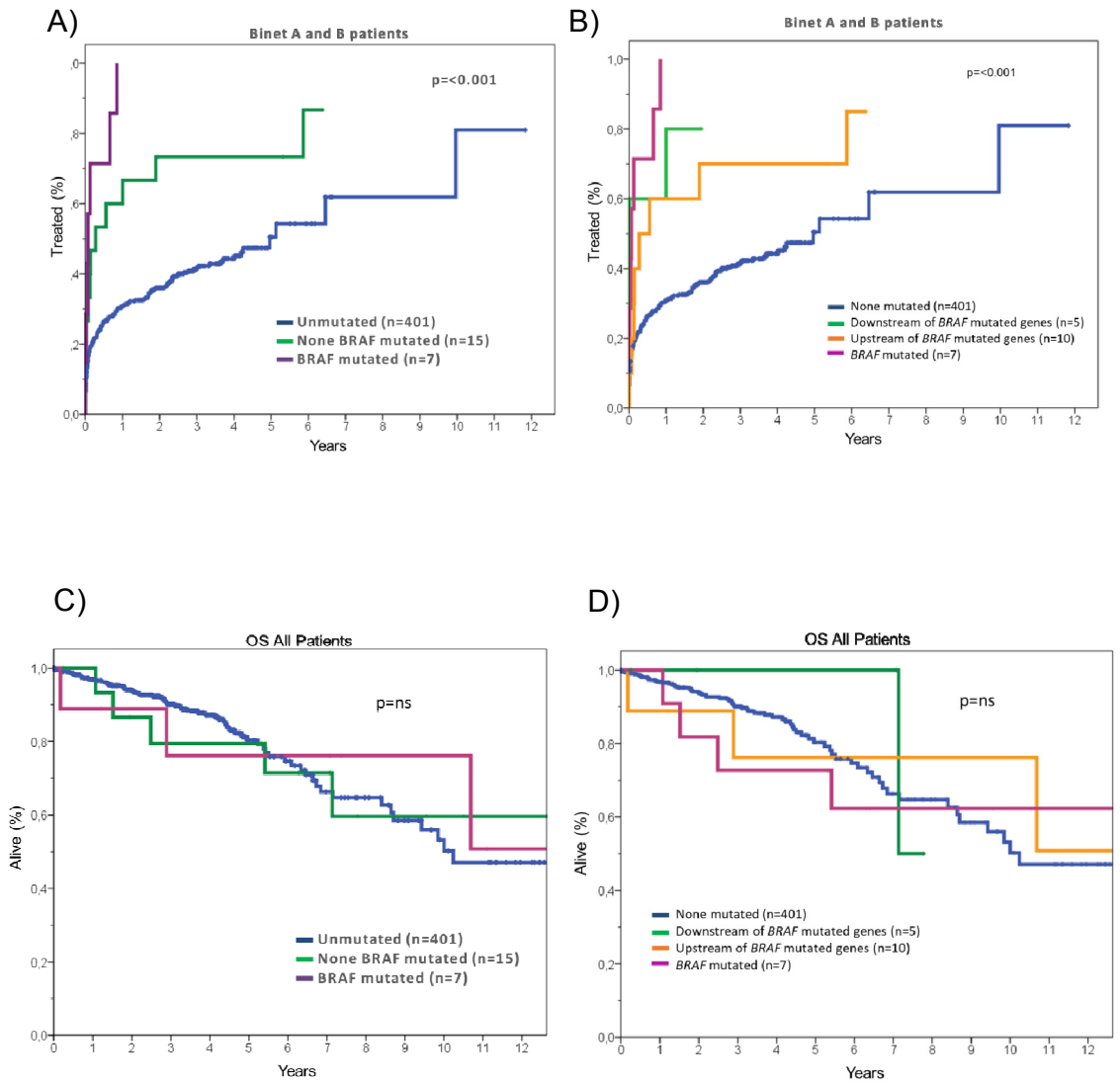

Figure S2. Outcome of patients according to the gene mutated and position of mutated genes in the RAS-BRAF-MAPK-ERK pathway. A) Time to first treatment in Binet A and B patients with mutations in *BRAF* (purple line), in genes different of *BRAF* (green line) or without mutations in RAS-BRAF-MAPK-ERK pathway (blue line). B) Time to first treatment in Binet A and B patients with mutations in *BRAF* (purple line), in genes upstream *BRAF* (orange line), downstream *BRAF* (green line), or without mutations in RAS-BRAF-MAPK-ERK pathway (blue line). C) Overall survival according to mutations in *BRAF* (purple line), in genes different of *BRAF* (green line) or without mutations in RAS-BRAF-MAPK-ERK pathway (blue line). D) Overall survival of patients according to mutations in *BRAF* (purple line), in genes upstream *BRAF* (orange line), downstream *BRAF* (green line), or without mutations in RAS-BRAF-MAPK-ERK pathway (blue line).

Table S1. Main clinical and biological characteristics of 452 patients included in the analysis

Characteristic	
Age, median (range)	62 years (18-93 years)
Sex (Male/Female), n (%)	276 (61%) / 176 (49%)
Binet Stage (A/B/C/unknown), n (%)	387 (86%) / 48 (11%) / 10 (2%) / 7 (1%)
Elevated LDH, n/total (%)	32/426 (7%)
Elevated beta 2 microglobulin, n/total (%)	126/391 (32%)
CD38 ≥30%, n/total (%)	106/426 (25%)
CD49d ≥30%, n/total (%)	101/303 (33%)
ZAP-70 ≥20%, n/total (%)	112/415 (27%)
Unmutated IGHV (≥98% homology), n/total (%)	166/445 (37%)
Trisomy 12, n/total (%)	54/321 (16.8%)
Del(11q)(q22.3), n/total (%)	26/320 (8%)
Del(17p)(p13.1), n/total (%)	12/321 (3.7%)
Median follow-up (range)	3.1 years (0.1-14.8)
Patients treated, n (%)	206 (46%)
Treatment, n (%)	206 (46%)
Chlorambucil	40 (20%)
Purine analogs monotherapy	8 (4%)
Fludarabine based polychemotherapy w/o rituximab	25 (12%)
Fludarabine-based polychematherapy with rituximab	93 (45%)
CHOP-like regimens	7 (3%)
Others	33 (16%)

Table S2. Upregulated gene sets in cases with mutations in the RAS-BRAF-MAPK-ERK pathway with c2.cp.Biocarta analysis.

	NAME	SIZE	NES	NOM p-val	FDR q-val
1	BIOCARTA_CDMAC_PATHWAY	16	2.09	0.002	0.001
2	BIOCARTA_CARDIACEGF_PATHWAY	18	2.03	0.000	0.002
3	BIOCARTA_TCR_PATHWAY	43	1.94	0.000	0.015
4	BIOCARTA_MET_PATHWAY	37	1.93	0.000	0.012
5	BIOCARTA_ETS_PATHWAY	18	1.93	0.000	0.010
6	**BIOCARTA_MAPK_PATHWAY**	**86**	**1.90**	**0.000**	**0.013**
7	BIOCARTA_BCELLSURVIVAL_PATHWAY	16	1.86	0.000	0.021
8	BIOCARTA_ARF_PATHWAY	17	1.83	0.005	0.029
9	BIOCARTA_TOB1_PATHWAY	19	1.79	0.007	0.046
10	BIOCARTA_GLEEVEC_PATHWAY	23	1.72	0.002	0.091
11	BIOCARTA_KERATINOCYTE_PATHWAY	46	1.72	0.005	0.085
12	BIOCARTA_STRESS_PATHWAY	25	1.71	0.005	0.085
13	BIOCARTA_TNFR1_PATHWAY	29	1.69	0.007	0.098
14	BIOCARTA_EPO_PATHWAY	19	1.68	0.012	0.096
15	BIOCARTA_PDGF_PATHWAY	32	1.67	0.010	0.097
16	BIOCARTA_TPO_PATHWAY	24	1.67	0.016	0.095
17	BIOCARTA_TGFB_PATHWAY	19	1.67	0.015	0.091
18	BIOCARTA_CCR5_PATHWAY	16	1.66	0.014	0.088
19	BIOCARTA_EGF_PATHWAY	31	1.66	0.005	0.088
20	BIOCARTA_IL12_PATHWAY	21	1.64	0.023	0.097
21	BIOCARTA_CTCF_PATHWAY	23	1.64	0.012	0.096
22	BIOCARTA_ERYTH_PATHWAY	15	1.62	0.018	0.106
23	BIOCARTA_CD40_PATHWAY	15	1.61	0.025	0.108
24	BIOCARTA_TEL_PATHWAY	18	1.61	0.028	0.108
25	BIOCARTA_MTOR_PATHWAY	23	1.61	0.027	0.106
26	BIOCARTA_NO2IL12_PATHWAY	17	1.61	0.019	0.103
27	BIOCARTA_NGF_PATHWAY	18	1.60	0.018	0.101
28	BIOCARTA_IL6_PATHWAY	22	1.60	0.014	0.098
29	BIOCARTA_LAIR_PATHWAY	17	1.60	0.030	0.098
30	BIOCARTA_IGF1_PATHWAY	21	1.59	0.018	0.102
31	BIOCARTA_NTHI_PATHWAY	24	1.59	0.019	0.100
32	BIOCARTA_IL2_PATHWAY	22	1.58	0.028	0.099
33	BIOCARTA_41BB_PATHWAY	17	1.58	0.030	0.103
34	BIOCARTA_HCMV_PATHWAY	17	1.57	0.028	0.104
35	BIOCARTA_G1_PATHWAY	28	1.54	0.036	0.128
36	BIOCARTA_VEGF_PATHWAY	29	1.54	0.040	0.128
37	BIOCARTA_INSULIN_PATHWAY	21	1.53	0.040	0.128
38	BIOCARTA_IL1R_PATHWAY	32	1.52	0.040	0.140
39	BIOCARTA_BCR_PATHWAY	34	1.51	0.036	0.148
40	BIOCARTA_CXCR4_PATHWAY	24	1.51	0.043	0.144
41	BIOCARTA_NKCELLS_PATHWAY	19	1.50	0.050	0.145
42	BIOCARTA_P38MAPK_PATHWAY	39	1.49	0.038	0.148
43	BIOCARTA_TOLL_PATHWAY	37	1.49	0.043	0.148
44	BIOCARTA_RACCYCD_PATHWAY	26	1.49	0.030	0.148

45	BIOCARTA_IL17_PATHWAY	15	1.48	0.047	0.150
46	BIOCARTA_TNFR2_PATHWAY	18	1.48	0.056	0.147
47	BIOCARTA_AGR_PATHWAY	36	1.46	0.055	0.161
48	BIOCARTA_IL3_PATHWAY	15	1.45	0.080	0.166
49	BIOCARTA_PPARA_PATHWAY	55	1.44	0.041	0.173
50	BIOCARTA_FAS_PATHWAY	30	1.43	0.070	0.180
51	BIOCARTA_RAC1_PATHWAY	23	1.43	0.080	0.178
52	BIOCARTA_PML_PATHWAY	17	1.42	0.085	0.186
53	BIOCARTA_MAL_PATHWAY	19	1.41	0.095	0.191
54	BIOCARTA_IL7_PATHWAY	17	1.41	0.075	0.191
55	BIOCARTA_HIVNEF_PATHWAY	58	1.40	0.052	0.204
56	BIOCARTA_IL22BP_PATHWAY	16	1.38	0.113	0.221
57	BIOCARTA_RAS_PATHWAY	23	1.38	0.108	0.218
58	BIOCARTA_AKT_PATHWAY	22	1.38	0.100	0.217
59	BIOCARTA_IL2RB_PATHWAY	38	1.35	0.091	0.245
60	BIOCARTA_NKT_PATHWAY	28	1.35	0.100	0.242
61	BIOCARTA_RARRXR_PATHWAY	15	1.34	0.155	0.252
62	BIOCARTA_PROTEASOME_PATHWAY	28	1.34	0.115	0.249
63	BIOCARTA_INTRINSIC_PATHWAY	23	1.33	0.129	0.252
64	BIOCARTA_MEF2D_PATHWAY	18	1.31	0.158	0.273
65	BIOCARTA_HIF_PATHWAY	15	1.31	0.156	0.270
66	BIOCARTA_CSK_PATHWAY	22	1.31	0.144	0.276
67	BIOCARTA_WNT_PATHWAY	26	1.30	0.140	0.277
68	BIOCARTA_ATM_PATHWAY	20	1.30	0.164	0.278
69	BIOCARTA_CTLA4_PATHWAY	19	1.30	0.142	0.278
70	BIOCARTA_VIP_PATHWAY	26	1.28	0.155	0.289
71	BIOCARTA_CALCINEURIN_PATHWAY	18	1.28	0.161	0.293
72	BIOCARTA_HDAC_PATHWAY	27	1.28	0.159	0.291
73	BIOCARTA_RELA_PATHWAY	16	1.27	0.198	0.296
74	BIOCARTA_PTDINS_PATHWAY	23	1.26	0.169	0.303
75	BIOCARTA_CELLCYCLE_PATHWAY	23	1.26	0.165	0.301
76	BIOCARTA_GPCR_PATHWAY	34	1.25	0.173	0.304
77	BIOCARTA_IGF1MTOR_PATHWAY	20	1.23	0.204	0.340
78	BIOCARTA_FMLP_PATHWAY	35	1.22	0.190	0.341
79	BIOCARTA_AMI_PATHWAY	20	1.21	0.220	0.347
80	BIOCARTA_SPPA_PATHWAY	22	1.21	0.234	0.351
81	BIOCARTA_CARM_ER_PATHWAY	34	1.20	0.219	0.356
82	BIOCARTA_NFKB_PATHWAY	23	1.20	0.227	0.353
83	BIOCARTA_EIF4_PATHWAY	24	1.19	0.237	0.363
84	BIOCARTA_TID_PATHWAY	19	1.19	0.250	0.360
85	BIOCARTA_GATA3_PATHWAY	16	1.18	0.277	0.370
86	BIOCARTA_TH1TH2_PATHWAY	19	1.17	0.251	0.383
87	BIOCARTA_FCER1_PATHWAY	38	1.16	0.243	0.395
88	BIOCARTA_AT1R_PATHWAY	32	1.15	0.299	0.409
89	BIOCARTA_GCR_PATHWAY	19	1.10	0.335	0.475
90	BIOCARTA_EIF_PATHWAY	16	1.10	0.356	0.473
91	BIOCARTA_PYK2_PATHWAY	28	1.10	0.316	0.470
92	BIOCARTA_ERK_PATHWAY	28	1.10	0.328	0.466

93	BIOCARTA_GSK3_PATHWAY	27	1.09	0.345	0.475
94	BIOCARTA_ECM_PATHWAY	24	1.08	0.346	0.481
95	BIOCARTA_MTA3_PATHWAY	17	1.07	0.372	0.491
96	BIOCARTA_P53HYPOXIA_PATHWAY	22	1.05	0.406	0.519
97	BIOCARTA_ERK5_PATHWAY	17	1.03	0.441	0.548
98	BIOCARTA_PAR1_PATHWAY	37	1.03	0.402	0.543
99	BIOCARTA_INFLAM_PATHWAY	28	1.03	0.438	0.538
100	BIOCARTA_LONGEVITY_PATHWAY	15	1.03	0.426	0.537
101	BIOCARTA_G2_PATHWAY	24	1.02	0.443	0.549
102	BIOCARTA_STATHMIN_PATHWAY	19	1.01	0.463	0.548
103	BIOCARTA_CERAMIDE_PATHWAY	22	0.99	0.489	0.581
104	BIOCARTA_ALK_PATHWAY	37	0.99	0.463	0.576
105	BIOCARTA_ACH_PATHWAY	16	0.98	0.490	0.583
106	BIOCARTA_P53_PATHWAY	16	0.97	0.502	0.595
107	BIOCARTA_CYTOKINE_PATHWAY	20	0.96	0.525	0.604
108	BIOCARTA_CK1_PATHWAY	17	0.96	0.503	0.604
109	BIOCARTA_RHO_PATHWAY	31	0.96	0.522	0.601
110	BIOCARTA_EDG1_PATHWAY	27	0.93	0.566	0.637
111	BIOCARTA_CDC42RAC_PATHWAY	15	0.93	0.544	0.638
112	BIOCARTA_UCALPAIN_PATHWAY	18	0.90	0.605	0.678
113	BIOCARTA_CHEMICAL_PATHWAY	22	0.89	0.611	0.683
114	BIOCARTA_NFAT_PATHWAY	53	0.89	0.634	0.678
115	BIOCARTA_CASPASE_PATHWAY	23	0.87	0.630	0.705
116	BIOCARTA_TFF_PATHWAY	21	0.86	0.658	0.722
117	BIOCARTA_ACTINY_PATHWAY	19	0.85	0.657	0.722
118	BIOCARTA_CHREBP2_PATHWAY	42	0.85	0.692	0.718
119	BIOCARTA_GH_PATHWAY	27	0.85	0.669	0.719
120	BIOCARTA_DEATH_PATHWAY	33	0.84	0.714	0.717
121	BIOCARTA_INTEGRIN_PATHWAY	38	0.83	0.709	0.725
122	BIOCARTA_HER2_PATHWAY	22	0.78	0.778	0.801
123	BIOCARTA_HSP27_PATHWAY	15	0.68	0.888	0.916
124	BIOCARTA_NDKDYNAMIN_PATHWAY	16	0.66	0.873	0.927
125	BIOCARTA_CCR3_PATHWAY	23	0.65	0.919	0.925
126	BIOCARTA_BARRESTIN_SRC_PATHWAY	15	0.64	0.889	0.925

Table S3. Upregulated gene sets in cases with mutations in the RAS-BRAF-MAPK-ERK pathway with c2.cp.KEGG analysis.

	NAME	SIZE	NES	NOM p-val	FDR q-val
1	KEGG_COLORECTAL_CANCER	62	2.13	0.000	0.001
2	KEGG_ACUTE_MYELOID_LEUKEMIA	57	2.06	0.000	0.001
3	KEGG_T_CELL_RECEPTOR_SIGNALING_PATHWAY	107	1.91	0.000	0.011
4	KEGG_CHRONIC_MYELOID_LEUKEMIA	72	1.88	0.000	0.011
5	**KEGG_MAPK_SIGNALING_PATHWAY**	**264**	**1.85**	**0.000**	**0.013**
6	KEGG_B_CELL_RECEPTOR_SIGNALING_PATHWAY	75	1.83	0.000	0.016
7	KEGG_LEUKOCYTE_TRANSENDOTHELIAL_MIGRATION	113	1.79	0.000	0.021
8	KEGG_ALDOSTERONE_REGULATED_SODIUM_REABSORPTION	41	1.76	0.003	0.028
9	KEGG_NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY	127	1.73	0.000	0.035
10	KEGG_MTOR_SIGNALING_PATHWAY	51	1.71	0.007	0.039
11	KEGG_SPLICEOSOME	124	1.71	0.000	0.036
12	KEGG_PANCREATIC_CANCER	70	1.70	0.002	0.036
13	KEGG_RENAL_CELL_CARCINOMA	70	1.68	0.005	0.040
14	KEGG_ENDOMETRIAL_CANCER	52	1.68	0.003	0.038
15	KEGG_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY	98	1.66	0.000	0.045
16	KEGG_MELANOMA	71	1.61	0.011	0.069
17	KEGG_FC_GAMMA_R_MEDIATED_PHAGOCYTOSIS	91	1.58	0.006	0.080
18	KEGG_LEISHMANIA_INFECTION	68	1.58	0.008	0.078
19	KEGG_NON_SMALL_CELL_LUNG_CANCER	54	1.58	0.034	0.077
20	KEGG_HEMATOPOIETIC_CELL_LINEAGE	85	1.57	0.006	0.078
21	KEGG_CELL_CYCLE	123	1.57	0.001	0.075
22	KEGG_PATHWAYS_IN_CANCER	325	1.55	0.000	0.086
23	KEGG_SMALL_CELL_LUNG_CANCER	84	1.53	0.013	0.092
24	KEGG_ERBB_SIGNALING_PATHWAY	86	1.52	0.014	0.101
25	KEGG_PHOSPHATIDYLINOSITOL_SIGNALING_SYSTEM	76	1.50	0.013	0.110
26	KEGG_BLADDER_CANCER	42	1.50	0.027	0.106
27	KEGG_THYROID_CANCER	29	1.48	0.055	0.120
28	KEGG_PRION_DISEASES	35	1.44	0.057	0.159
29	KEGG_TGF_BETA_SIGNALING_PATHWAY	85	1.41	0.031	0.188
30	KEGG_GLIOMA	64	1.41	0.051	0.188
31	KEGG_ENDOCYTOSIS	180	1.40	0.017	0.185
32	KEGG_RIG_I_LIKE_RECEPTOR_SIGNALING_PATHWAY	69	1.40	0.061	0.186
33	KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY	66	1.39	0.066	0.186
34	KEGG_NOTCH_SIGNALING_PATHWAY	47	1.36	0.091	0.222
35	KEGG_PRIMARY_IMMUNODEFICIENCY	35	1.36	0.096	0.226
36	KEGG_INOSITOL_PHOSPHATE_METABOLISM	54	1.35	0.085	0.230
37	KEGG_REGULATION_OF_ACTIN_CYTOSKELETON	208	1.35	0.024	0.230
38	KEGG_ARRHYTHMOGENIC_RIGHT_VENTRICULAR _CARDIOMYOPATHY_ARVC	74	1.34	0.073	0.236
39	KEGG_STEROID_BIOSYNTHESIS	15	1.34	0.154	0.230
40	KEGG_NEUROTROPHIN_SIGNALING_PATHWAY	125	1.34	0.055	0.227
41	KEGG_PROSTATE_CANCER	88	1.30	0.084	0.267
42	KEGG_JAK_STAT_SIGNALING_PATHWAY	150	1.30	0.070	0.276
43	KEGG_OTHER_GLYCAN_DEGRADATION	16	1.29	0.182	0.274
44	KEGG_RIBOSOME	85	1.29	0.102	0.279

45	KEGG_WNT_SIGNALING_PATHWAY	150	1.27	0.086	0.308
46	KEGG_CYTOSOLIC_DNA_SENSING_PATHWAY	51	1.26	0.128	0.312
47	KEGG_SPHINGOLIPID_METABOLISM	38	1.22	0.180	0.377
48	KEGG_FOCAL_ADHESION	196	1.20	0.120	0.409
49	KEGG_ECM_RECEPTOR_INTERACTION	83	1.19	0.178	0.426
50	KEGG_EPITHELIAL_CELL_SIGNALING_IN_ HELICOBACTER_PYLORI_INFECTION	68	1.19	0.197	0.422
51	KEGG_CELL_ADHESION_MOLECULES_CAMS	130	1.18	0.174	0.433
52	KEGG_FC_EPSILON_RI_SIGNALING_PATHWAY	76	1.17	0.211	0.449
53	KEGG_VEGF_SIGNALING_PATHWAY	73	1.16	0.225	0.466
54	KEGG_HYPERTROPHIC_CARDIOMYOPATHY_HCM	83	1.16	0.212	0.458
55	KEGG_FRUCTOSE_AND_MANNOSE_METABOLISM	34	1.14	0.303	0.481
56	KEGG_INSULIN_SIGNALING_PATHWAY	135	1.10	0.259	0.568
57	KEGG_CHEMOKINE_SIGNALING_PATHWAY	179	1.10	0.267	0.569
58	KEGG_RNA_DEGRADATION	57	1.09	0.315	0.565
59	KEGG_DILATED_CARDIOMYOPATHY	90	1.09	0.296	0.556
60	KEGG_LYSOSOME	120	1.08	0.310	0.571
61	KEGG_P53_SIGNALING_PATHWAY	67	1.08	0.332	0.574
62	KEGG_NOD_LIKE_RECEPTOR_SIGNALING_PATHWAY	62	1.08	0.338	0.565
63	KEGG_PENTOSE_PHOSPHATE_PATHWAY	27	1.06	0.360	0.589
64	KEGG_PROGESTERONE_MEDIATED_OOCYTE_MATURATION	84	1.05	0.368	0.618
65	KEGG_UBIQUITIN_MEDIATED_PROTEOLYSIS	134	1.03	0.401	0.647
66	KEGG_LYSINE_DEGRADATION	44	1.03	0.397	0.642
67	KEGG_APOPTOSIS	87	1.03	0.428	0.640
68	KEGG_TIGHT_JUNCTION	131	1.02	0.415	0.648
69	KEGG_BASAL_CELL_CARCINOMA	55	1.02	0.411	0.645
70	KEGG_TYPE_II_DIABETES_MELLITUS	46	1.02	0.418	0.637
71	KEGG_GLYCOLYSIS_GLUCONEOGENESIS	62	1.02	0.426	0.629
72	KEGG_RIBOFLAVIN_METABOLISM	16	1.01	0.454	0.629
73	KEGG_PYRIMIDINE_METABOLISM	93	1.01	0.438	0.625
74	KEGG_VIBRIO_CHOLERAE_INFECTION	54	1.01	0.416	0.620
75	KEGG_AMINOACYL_TRNA_BIOSYNTHESIS	41	0.97	0.516	0.708
76	KEGG_ADHERENS_JUNCTION	73	0.96	0.507	0.710
77	KEGG_GALACTOSE_METABOLISM	26	0.96	0.516	0.707
78	KEGG_PROTEASOME	44	0.96	0.533	0.701
79	KEGG_PANTOTHENATE_AND_COA_BIOSYNTHESIS	16	0.95	0.534	0.708
80	KEGG_PROTEIN_EXPORT	23	0.95	0.535	0.711
81	KEGG_NICOTINATE_AND_NICOTINAMIDE_METABOLISM	23	0.94	0.547	0.729
82	KEGG_CARDIAC_MUSCLE_CONTRACTION	74	0.94	0.574	0.724
83	KEGG_MATURITY_ONSET_DIABETES_OF_THE_YOUNG	24	0.93	0.562	0.734
84	KEGG_GLYCOSPHINGOLIPID_BIOSYNTHESIS _GANGLIO_SERIES	15	0.90	0.619	0.794
85	KEGG_GLYCEROPHOSPHOLIPID_METABOLISM	73	0.89	0.667	0.797
86	KEGG_REGULATION_OF_AUTOPHAGY	31	0.88	0.631	0.799
87	KEGG_PROXIMAL_TUBULE_BICARBONATE _RECLAMATION	23	0.88	0.631	0.791
88	KEGG_OOCYTE_MEIOSIS	110	0.88	0.705	0.784
89	KEGG_PHENYLALANINE_METABOLISM	18	0.87	0.644	0.809
90	KEGG_GLYCEROLIPID_METABOLISM	48	0.84	0.734	0.863
91	KEGG_GLYCOSAMINOGLYCAN_BIOSYNTHESIS_ CHONDROITIN_SULFATE	22	0.82	0.720	0.884

92	KEGG_RNA_POLYMERASE	27	0.81	0.749	0.882
93	KEGG_CYSTEINE_AND_METHIONINE_METABOLISM	34	0.80	0.762	0.895
94	KEGG_ALZHEIMERS_DISEASE	158	0.79	0.895	0.907
95	KEGG_COMPLEMENT_AND_COAGULATION_CASCADES	67	0.77	0.842	0.925
96	KEGG_LONG_TERM_DEPRESSION	67	0.77	0.856	0.920
97	KEGG_TERPENOID_BACKBONE_BIOSYNTHESIS	15	0.76	0.769	0.915
98	KEGG_BASAL_TRANSCRIPTION_FACTORS	33	0.76	0.803	0.906
99	KEGG_LONG_TERM_POTENTIATION	70	0.74	0.906	0.934
100	KEGG_BASE_EXCISION_REPAIR	33	0.73	0.868	0.927
101	KEGG_ETHER_LIPID_METABOLISM	31	0.71	0.855	0.941
102	KEGG_DRUG_METABOLISM_OTHER_ENZYMES	42	0.69	0.925	0.948
103	KEGG_CITRATE_CYCLE_TCA_CYCLE	30	0.68	0.907	0.950
104	KEGG_AXON_GUIDANCE	129	0.66	0.990	0.952

Table S4. Genes of the Biocarta-MAPK pathway

	GENE SYMBOL	GENE_TITLE	CORE ENRICHMENT
1	ARAF	v-raf murine sarcoma 3611 viral oncogene homolog	Yes
2	ATF2	activating transcription factor 2	No
3	BRAF	v-raf murine sarcoma viral oncogene homolog B1	No
4	CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha	No
5	CHUK	conserved helix-loop-helix ubiquitous kinase	Yes
6	CREB1	cAMP responsive element binding protein 1	No
7	DAXX	death-associated protein 6	No
8	ELK1	ELK1, member of ETS oncogene family	No
9	FOS	v-fos FBJ murine osteosarcoma viral oncogene homolog	Yes
10	GRB2	growth factor receptor-bound protein 2	No
11	HRAS	v-Ha-ras Harvey rat sarcoma viral oncogene homolog	Yes
12	IKBKB	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta	No
13	JUN	jun oncogene	Yes
14	MAP2K1	mitogen-activated protein kinase kinase 1	No
15	MAP2K2	mitogen-activated protein kinase kinase 2	Yes
16	MAP2K3	mitogen-activated protein kinase kinase 3	Yes
17	MAP2K4	mitogen-activated protein kinase kinase 4	No
18	MAP2K5	mitogen-activated protein kinase kinase 5	Yes
19	MAP2K6	mitogen-activated protein kinase kinase 6	Yes
20	MAP2K7	mitogen-activated protein kinase kinase 7	No
21	MAP3K1	mitogen-activated protein kinase kinase kinase 1	Yes
22	MAP3K10	mitogen-activated protein kinase kinase kinase 10	No
23	MAP3K11	mitogen-activated protein kinase kinase kinase 11	No
24	MAP3K12	mitogen-activated protein kinase kinase kinase 12	Yes
25	MAP3K13	mitogen-activated protein kinase kinase kinase 13	No
26	MAP3K14	mitogen-activated protein kinase kinase kinase 14	No
27	MAP3K2	mitogen-activated protein kinase kinase kinase 2	No
28	MAP3K3	mitogen-activated protein kinase kinase kinase 3	No
29	MAP3K4	mitogen-activated protein kinase kinase kinase 4	Yes
30	MAP3K5	mitogen-activated protein kinase kinase kinase 5	No
31	MAP3K6	mitogen-activated protein kinase kinase kinase 6	No
32	MAP3K7	mitogen-activated protein kinase kinase kinase 7	Yes
33	MAP3K8	mitogen-activated protein kinase kinase kinase 8	Yes
34	MAP3K9	mitogen-activated protein kinase kinase kinase 9	No
35	MAP4K1	mitogen-activated protein kinase kinase kinase kinase 1	No
36	MAP4K2	mitogen-activated protein kinase kinase kinase kinase 2	Yes
37	MAP4K3	mitogen-activated protein kinase kinase kinase kinase 3	Yes
38	MAP4K4	mitogen-activated protein kinase kinase kinase kinase 4	Yes
39	MAP4K5	mitogen-activated protein kinase kinase kinase kinase 5	No
40	MAPK1	mitogen-activated protein kinase 1	No
41	MAPK10	mitogen-activated protein kinase 10	No
42	MAPK11	mitogen-activated protein kinase 11	No
43	MAPK12	mitogen-activated protein kinase 12	No
44	MAPK13	mitogen-activated protein kinase 13	No
45	MAPK14	mitogen-activated protein kinase 14	No

46	MAPK3	mitogen-activated protein kinase 3	No
47	MAPK4	mitogen-activated protein kinase 4	Yes
48	MAPK6	mitogen-activated protein kinase 6	Yes
49	MAPK7	mitogen-activated protein kinase 7	No
50	MAPK8	mitogen-activated protein kinase 8	No
51	MAPK9	mitogen-activated protein kinase 9	No
52	MAPKAPK2	mitogen-activated protein kinase-activated protein kinase 2	No
53	MAPKAPK3	mitogen-activated protein kinase-activated protein kinase 3	No
54	MAPKAPK5	mitogen-activated protein kinase-activated protein kinase 5	Yes
55	MAX	MYC associated factor X	No
56	MEF2A	MADS box transcription enhancer factor 2, polypeptide A (myocyte enhancer factor 2A)	No
57	MEF2C	MADS box transcription enhancer factor 2, polypeptide C (myocyte enhancer factor 2C)	No
58	MEF2D	MADS box transcription enhancer factor 2, polypeptide D (myocyte enhancer factor 2D)	Yes
59	MKNK1	MAP kinase interacting serine/threonine kinase 1	No
60	MKNK2	MAP kinase interacting serine/threonine kinase 2	Yes
61	MYC	v-myc myelocytomatosis viral oncogene homolog (avian)	Yes
62	NFKB1	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1 (p105)	Yes
63	NFKBIA	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha	No
64	PAK1	p21/Cdc42/Rac1-activated kinase 1 (STE20 homolog, yeast)	Yes
65	PAK2	p21 (CDKN1A)-activated kinase 2	No
66	RAC1	ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1)	Yes
67	RAF1	v-raf-1 murine leukemia viral oncogene homolog 1	No
68	RAPGEF2	Rap guanine nucleotide exchange factor (GEF) 2	No
69	RELA	v-rel reticuloendotheliosis viral oncogene homolog A, nuclear factor of kappa light polypeptide gene enhancer in B-cells 3, p65 (avian)	Yes
70	RIPK1	receptor (TNFRSF)-interacting serine-threonine kinase 1	Yes
71	RPS6KA1	ribosomal protein S6 kinase, 90kDa, polypeptide 1	No
72	RPS6KA2	ribosomal protein S6 kinase, 90kDa, polypeptide 2	No
73	RPS6KA3	ribosomal protein S6 kinase, 90kDa, polypeptide 3	No
74	RPS6KA4	ribosomal protein S6 kinase, 90kDa, polypeptide 4	Yes
75	RPS6KA5	ribosomal protein S6 kinase, 90kDa, polypeptide 5	Yes
76	RPS6KB1	ribosomal protein S6 kinase, 70kDa, polypeptide 1	Yes
77	RPS6KB2	ribosomal protein S6 kinase, 70kDa, polypeptide 2	No
78	SHC1	SHC (Src homology 2 domain containing) transforming protein 1	Yes
79	SP1	Sp1 transcription factor	Yes
80	STAT1	signal transducer and activator of transcription 1, 91kDa	No
81	TGFB1	transforming growth factor, beta 1 (Camurati-Engelmann disease)	Yes
82	TGFB2	transforming growth factor, beta 2	No
83	TGFB3	transforming growth factor, beta 3	No
84	TGFBR1	transforming growth factor, beta receptor I (activin A receptor type II-like kinase, 53kDa)	Yes
85	TRADD	TNFRSF1A-associated via death domain	No
86	TRAF2	TNF receptor-associated factor 2	Yes

Table S5. Genes of the KEGG-MAPK SIGNALING pathway

	GENE SYMBOL	GENE_TITLE	CORE ENRICHMENT
1	AKT1	v-akt murine thymoma viral oncogene homolog 1	No
2	AKT2	v-akt murine thymoma viral oncogene homolog 2	No
3	AKT3	v-akt murine thymoma viral oncogene homolog 3 (protein kinase B, gamma)	Yes
4	ARRB1	arrestin, beta 1	No
5	ARRB2	arrestin, beta 2	Yes
6	ATF2	activating transcription factor 2	No
7	ATF4	activating transcription factor 4 (tax-responsive enhancer element B67)	Yes
8	BDNF	brain-derived neurotrophic factor	No
9	BRAF	v-raf murine sarcoma viral oncogene homolog B1	No
10	CACNA1A	calcium channel, voltage-dependent, P/Q type, alpha 1A subunit	No
11	CACNA1B	calcium channel, voltage-dependent, L type, alpha 1B subunit	No
12	CACNA1C	calcium channel, voltage-dependent, L type, alpha 1C subunit	No
13	CACNA1D	calcium channel, voltage-dependent, L type, alpha 1D subunit	No
14	CACNA1E	calcium channel, voltage-dependent, alpha 1E subunit	No
15	CACNA1F	calcium channel, voltage-dependent, alpha 1F subunit	No
16	CACNA1G	calcium channel, voltage-dependent, alpha 1G subunit	No
17	CACNA1H	calcium channel, voltage-dependent, alpha 1H subunit	No
18	CACNA1I	calcium channel, voltage-dependent, alpha 1I subunit	No
19	CACNA1S	calcium channel, voltage-dependent, L type, alpha 1S subunit	No
20	CACNA2D1	calcium channel, voltage-dependent, alpha 2/delta subunit 1	No
21	CACNA2D2	calcium channel, voltage-dependent, alpha 2/delta subunit 2	No
22	CACNA2D3	calcium channel, voltage-dependent, alpha 2/delta 3 subunit	No
23	CACNA2D4	calcium channel, voltage-dependent, alpha 2/delta subunit 4	Yes
24	CACNB1	calcium channel, voltage-dependent, beta 1 subunit	No
25	CACNB2	calcium channel, voltage-dependent, beta 2 subunit	Yes
26	CACNB3	calcium channel, voltage-dependent, beta 3 subunit	No
27	CACNB4	calcium channel, voltage-dependent, beta 4 subunit	No
28	CACNG1	calcium channel, voltage-dependent, gamma subunit 1	No
29	CACNG2	calcium channel, voltage-dependent, gamma subunit 2	No
30	CACNG3	calcium channel, voltage-dependent, gamma subunit 3	No
31	CACNG4	calcium channel, voltage-dependent, gamma subunit 4	No
32	CACNG5	calcium channel, voltage-dependent, gamma subunit 5	No
33	CACNG6	calcium channel, voltage-dependent, gamma subunit 6	No
34	CACNG7	calcium channel, voltage-dependent, gamma subunit 7	No
35	CACNG8	calcium channel, voltage-dependent, gamma subunit 8	No
36	CASP3	caspase 3, apoptosis-related cysteine peptidase	No
37	CD14	CD14 molecule	Yes
38	CDC25B	cell division cycle 25B	No
39	CDC42	cell division cycle 42 (GTP binding protein, 25kDa)	No
40	CHP	-	No
41	CHP2	-	No
42	CHUK	conserved helix-loop-helix ubiquitous kinase	Yes
43	CRK	v-crk sarcoma virus CT10 oncogene homolog (avian)	No
44	CRKL	v-crk sarcoma virus CT10 oncogene homolog (avian)-like	No

45	DAXX	death-associated protein 6	No
46	DDIT3	DNA-damage-inducible transcript 3	Yes
47	DUSP1	dual specificity phosphatase 1	Yes
48	DUSP10	dual specificity phosphatase 10	Yes
49	DUSP14	dual specificity phosphatase 14	No
50	DUSP16	dual specificity phosphatase 16	No
51	DUSP2	dual specificity phosphatase 2	Yes
52	DUSP3	dual specificity phosphatase 3 (vaccinia virus phosphatase VH1-related)	No
53	DUSP4	dual specificity phosphatase 4	No
54	DUSP5	dual specificity phosphatase 5	Yes
55	DUSP6	dual specificity phosphatase 6	Yes
56	DUSP7	dual specificity phosphatase 7	No
57	DUSP8	dual specificity phosphatase 8	Yes
58	DUSP9	dual specificity phosphatase 9	No
59	ECSIT	ECSIT homolog (Drosophila)	Yes
60	EGF	epidermal growth factor (beta-urogastrone)	No
61	EGFR	epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) oncogene homolog, avian)	No
62	ELK1	ELK1, member of ETS oncogene family	No
63	ELK4	ELK4, ETS-domain protein (SRF accessory protein 1)	No
64	FAS	Fas (TNF receptor superfamily, member 6)	No
65	FASLG	Fas ligand (TNF superfamily, member 6)	No
66	FGF1	fibroblast growth factor 1 (acidic)	No
67	FGF10	fibroblast growth factor 10	No
68	FGF11	fibroblast growth factor 11	No
69	FGF12	fibroblast growth factor 12	No
70	FGF13	fibroblast growth factor 13	No
71	FGF14	fibroblast growth factor 14	No
72	FGF16	fibroblast growth factor 16	No
73	FGF17	fibroblast growth factor 17	No
74	FGF18	fibroblast growth factor 18	No
75	FGF19	fibroblast growth factor 19	No
76	FGF2	fibroblast growth factor 2 (basic)	Yes
77	FGF20	fibroblast growth factor 20	No
78	FGF21	fibroblast growth factor 21	No
79	FGF22	fibroblast growth factor 22	No
80	FGF23	fibroblast growth factor 23	No
81	FGF3	fibroblast growth factor 3 (murine mammary tumor virus integration site (v-int-2) oncogene homolog)	No
82	FGF4	fibroblast growth factor 4 (heparin secretory transforming protein 1, Kaposi sarcoma oncogene)	No
83	FGF5	fibroblast growth factor 5	No
84	FGF6	fibroblast growth factor 6	No
85	FGF7	fibroblast growth factor 7 (keratinocyte growth factor)	No
86	FGF8	fibroblast growth factor 8 (androgen-induced)	No
87	FGF9	fibroblast growth factor 9 (glia-activating factor)	No
88	FGFR1	fibroblast growth factor receptor 1 (fms-related tyrosine kinase 2, Pfeiffer syndrome)	No
89	FGFR2	ffer syndrome, Jackson-Weiss syndrome)	No
90	FGFR3	fibroblast growth factor receptor 3 (achondroplasia, thanatophoric dwarfism)	No

91	FGFR4	fibroblast growth factor receptor 4	No
92	FLNA	filamin A, alpha (actin binding protein 280)	No
93	FLNB	filamin B, beta (actin binding protein 278)	Yes
94	FLNC	filamin C, gamma (actin binding protein 280)	No
95	FOS	v-fos FBJ murine osteosarcoma viral oncogene homolog	Yes
96	GADD45A	growth arrest and DNA-damage-inducible, alpha	No
97	GADD45B	growth arrest and DNA-damage-inducible, beta	Yes
98	GADD45G	growth arrest and DNA-damage-inducible, gamma	No
99	GNA12	guanine nucleotide binding protein (G protein) alpha 12	No
100	GNG12	guanine nucleotide binding protein (G protein), gamma 12	No
101	GRB2	growth factor receptor-bound protein 2	No
102	HRAS	v-Ha-ras Harvey rat sarcoma viral oncogene homolog	Yes
103	HSPA1A	heat shock 70kDa protein 1A	No
104	HSPA1B	heat shock 70kDa protein 1B	Yes
105	HSPA1L	heat shock 70kDa protein 1-like	No
106	HSPA2	heat shock 70kDa protein 2	No
107	HSPA6	heat shock 70kDa protein 6 (HSP70B')	No
108	HSPA8	heat shock 70kDa protein 8	Yes
109	HSPB1	heat shock 27kDa protein 1	No
110	IKBKB	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta	No
111	IKBKG	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma	No
112	IL1A	interleukin 1, alpha	No
113	IL1B	interleukin 1, beta	No
114	IL1R1	interleukin 1 receptor, type I	No
115	IL1R2	interleukin 1 receptor, type II	No
116	JUN	jun oncogene	Yes
117	JUND	jun D proto-oncogene	Yes
118	KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog	Yes
119	MAP2K1	mitogen-activated protein kinase kinase 1	No
120	MAP2K2	mitogen-activated protein kinase kinase 2	Yes
121	MAP2K3	mitogen-activated protein kinase kinase 3	Yes
122	MAP2K4	mitogen-activated protein kinase kinase 4	No
123	MAP2K5	mitogen-activated protein kinase kinase 5	Yes
124	MAP2K6	mitogen-activated protein kinase kinase 6	No
125	MAP2K7	mitogen-activated protein kinase kinase 7	No
126	MAP3K1	mitogen-activated protein kinase kinase kinase 1	Yes
127	MAP3K11	mitogen-activated protein kinase kinase kinase 11	No
128	MAP3K12	mitogen-activated protein kinase kinase kinase 12	Yes
129	MAP3K13	mitogen-activated protein kinase kinase kinase 13	No
130	MAP3K14	mitogen-activated protein kinase kinase kinase 14	No
131	MAP3K2	mitogen-activated protein kinase kinase kinase 2	No
132	MAP3K3	mitogen-activated protein kinase kinase kinase 3	No
133	MAP3K4	mitogen-activated protein kinase kinase kinase 4	Yes
134	MAP3K5	mitogen-activated protein kinase kinase kinase 5	No
135	MAP3K6	mitogen-activated protein kinase kinase kinase 6	No
136	MAP3K7	mitogen-activated protein kinase kinase kinase 7	No

137	MAP3K8	mitogen-activated protein kinase kinase kinase 8	Yes
138	MAP4K1	mitogen-activated protein kinase kinase kinase kinase 1	No
139	MAP4K2	mitogen-activated protein kinase kinase kinase kinase 2	No
140	MAP4K3	mitogen-activated protein kinase kinase kinase kinase 3	Yes
141	MAP4K4	mitogen-activated protein kinase kinase kinase kinase 4	Yes
142	MAPK1	mitogen-activated protein kinase 1	No
143	MAPK10	mitogen-activated protein kinase 10	No
144	MAPK11	mitogen-activated protein kinase 11	No
145	MAPK12	mitogen-activated protein kinase 12	No
146	MAPK13	mitogen-activated protein kinase 13	No
147	MAPK14	mitogen-activated protein kinase 14	No
148	MAPK3	mitogen-activated protein kinase 3	No
149	MAPK7	mitogen-activated protein kinase 7	No
150	MAPK8	mitogen-activated protein kinase 8	No
151	MAPK8IP1	mitogen-activated protein kinase 8 interacting protein 1	No
152	MAPK8IP2	mitogen-activated protein kinase 8 interacting protein 2	No
153	MAPK8IP3	mitogen-activated protein kinase 8 interacting protein 3	Yes
154	MAPK9	mitogen-activated protein kinase 9	No
155	MAPKAPK2	mitogen-activated protein kinase-activated protein kinase 2	No
156	MAPKAPK3	mitogen-activated protein kinase-activated protein kinase 3	No
157	MAPKAPK5	mitogen-activated protein kinase-activated protein kinase 5	Yes
158	MAPT	microtubule-associated protein tau	No
159	MAX	MYC associated factor X	No
160	MECOM		No
161	MEF2C	MADS box transcription enhancer factor 2, polypeptide C (myocyte enhancer factor 2C)	No
162	MKNK1	MAP kinase interacting serine/threonine kinase 1	No
163	MKNK2	MAP kinase interacting serine/threonine kinase 2	No
164	MOS	v-mos Moloney murine sarcoma viral oncogene homolog	No
165	MRAS	muscle RAS oncogene homolog	No
166	MYC	v-myc myelocytomatosis viral oncogene homolog (avian)	Yes
167	NF1	neurofibromin 1 (neurofibromatosis, von Recklinghausen disease, Watson disease)	Yes
168	NFATC2	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 2	No
169	NFATC4	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 4	No
170	NFKB1	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1 (p105)	Yes
171	NFKB2	nuclear factor of kappa light polypeptide gene enhancer in B-cells 2 (p49/p100)	No
172	NGF		No
173	NLK	nemo-like kinase	No
174	NR4A1	nuclear receptor subfamily 4, group A, member 1	Yes
175	NRAS	neuroblastoma RAS viral (v-ras) oncogene homolog	No
176	NTF3	neurotrophin 3	No
177	NTF4	null	No
178	NTRK1	neurotrophic tyrosine kinase, receptor, type 1	No
179	NTRK2	neurotrophic tyrosine kinase, receptor, type 2	No
180	PAK1	p21/Cdc42/Rac1-activated kinase 1 (STE20 homolog, yeast)	Yes
181	PAK2	p21 (CDKN1A)-activated kinase 2	No
182	PDGFA	platelet-derived growth factor alpha polypeptide	Yes

183	PDGFB	platelet-derived growth factor beta polypeptide (simian sarcoma viral (v-sis) oncogene homolog)	No
184	PDGFRA	platelet-derived growth factor receptor, alpha polypeptide	No
185	PDGFRB	platelet-derived growth factor receptor, beta polypeptide	No
186	PLA2G10	phospholipase A2, group X	No
187	PLA2G12A	phospholipase A2, group XIIA	No
188	PLA2G12B	phospholipase A2, group XIIB	No
189	PLA2G1B	phospholipase A2, group IB (pancreas)	No
190	PLA2G2A	phospholipase A2, group IIA (platelets, synovial fluid)	No
191	PLA2G2C	phospholipase A2, group IIC	No
192	PLA2G2D	phospholipase A2, group IID	No
193	PLA2G2E	phospholipase A2, group IIE	No
194	PLA2G2F	phospholipase A2, group IIF	No
195	PLA2G3	phospholipase A2, group III	No
196	PLA2G4A	phospholipase A2, group IVA (cytosolic, calcium-dependent)	No
197	PLA2G4E	phospholipase A2, group IVE	No
198	PLA2G5	phospholipase A2, group V	No
199	PLA2G6	phospholipase A2, group VI (cytosolic, calcium-independent)	No
200	PPM1A	protein phosphatase 1A (formerly 2C), magnesium-dependent, alpha isoform	No
201	PPM1B	protein phosphatase 1B (formerly 2C), magnesium-dependent, beta isoform	Yes
202	PPP3CA	protein phosphatase 3 (formerly 2B), catalytic subunit, alpha isoform (calcineurin A alpha)	No
203	PPP3CB	protein phosphatase 3 (formerly 2B), catalytic subunit, beta isoform (calcineurin A beta)	No
204	PPP3CC	protein phosphatase 3 (formerly 2B), catalytic subunit, gamma isoform (calcineurin A gamma)	No
205	PPP3R1	protein phosphatase 3 (formerly 2B), regulatory subunit B, 19kDa, alpha isoform (calcineurin B, type I)	No
206	PPP3R2	protein phosphatase 3 (formerly 2B), regulatory subunit B, 19kDa, beta isoform (calcineurin B, type II)	No
207	PPP5C	protein phosphatase 5, catalytic subunit	Yes
208	PRKACA	protein kinase, cAMP-dependent, catalytic, alpha	No
209	PRKACB	protein kinase, cAMP-dependent, catalytic, beta	No
210	PRKACG	protein kinase, cAMP-dependent, catalytic, gamma	No
211	PRKCA	protein kinase C, alpha	Yes
212	PRKCB		No
213	PRKCG	protein kinase C, gamma	No
214	PRKX	protein kinase, X-linked	No
215	PTPN5	protein tyrosine phosphatase, non-receptor type 5 (striatum-enriched)	No
216	PTPN7	protein tyrosine phosphatase, non-receptor type 7	Yes
217	PTPRR	protein tyrosine phosphatase, receptor type, R	No
218	RAC1	ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1)	Yes
219	RAC2	ras-related C3 botulinum toxin substrate 2 (rho family, small GTP binding protein Rac2)	No
220	RAC3	ras-related C3 botulinum toxin substrate 3 (rho family, small GTP binding protein Rac3)	No
221	RAF1	v-raf-1 murine leukemia viral oncogene homolog 1	No
222	RAP1A	RAP1A, member of RAS oncogene family	No
223	RAP1B	RAP1B, member of RAS oncogene family	Yes
224	RAPGEF2	Rap guanine nucleotide exchange factor (GEF) 2	No
225	RASA1	RAS p21 protein activator (GTPase activating protein) 1	Yes
226	RASA2	RAS p21 protein activator 2	Yes

227	RASGRF1	Ras protein-specific guanine nucleotide-releasing factor 1	No
228	RASGRF2	Ras protein-specific guanine nucleotide-releasing factor 2	No
229	RASGRP1	RAS guanyl releasing protein 1 (calcium and DAG-regulated)	No
230	RASGRP2	RAS guanyl releasing protein 2 (calcium and DAG-regulated)	No
231	RASGRP3	RAS guanyl releasing protein 3 (calcium and DAG-regulated)	No
232	RASGRP4	RAS guanyl releasing protein 4	No
233	RELA	v-rel reticuloendotheliosis viral oncogene homolog A, nuclear factor of kappa light polypeptide gene enhancer in B-cells 3, p65 (avian)	Yes
234	RELB	v-rel reticuloendotheliosis viral oncogene homolog B, nuclear factor of kappa light polypeptide gene enhancer in B-cells 3 (avian)	Yes
235	RPS6KA1	ribosomal protein S6 kinase, 90kDa, polypeptide 1	No
236	RPS6KA2	ribosomal protein S6 kinase, 90kDa, polypeptide 2	No
237	RPS6KA3	ribosomal protein S6 kinase, 90kDa, polypeptide 3	No
238	RPS6KA4	ribosomal protein S6 kinase, 90kDa, polypeptide 4	No
239	RPS6KA5	ribosomal protein S6 kinase, 90kDa, polypeptide 5	No
240	RPS6KA6	ribosomal protein S6 kinase, 90kDa, polypeptide 6	No
241	RRAS	related RAS viral (r-ras) oncogene homolog	No
242	RRAS2	related RAS viral (r-ras) oncogene homolog 2	No
243	SOS1	son of sevenless homolog 1 (Drosophila)	No
244	SOS2	son of sevenless homolog 2 (Drosophila)	No
245	SRF	serum response factor (c-fos serum response element-binding transcription factor)	No
246	STK3	serine/threonine kinase 3 (STE20 homolog, yeast)	No
247	STK4	serine/threonine kinase 4	No
248	STMN1	stathmin 1/oncoprotein 18	No
249	TAB1	-	No
250	TAB2	-	No
251	TAOK1	TAO kinase 1	No
252	TAOK2	TAO kinase 2	No
253	TAOK3	TAO kinase 3	Yes
254	TGFB1	transforming growth factor, beta 1 (Camurati-Engelmann disease)	Yes
255	TGFB2	transforming growth factor, beta 2	No
256	TGFB3	transforming growth factor, beta 3	No
257	TGFBR1	transforming growth factor, beta receptor I (activin A receptor type II-like kinase, 53kDa)	Yes
258	TGFBR2	transforming growth factor, beta receptor II (70/80kDa)	No
259	TNF	tumor necrosis factor (TNF superfamily, member 2)	Yes
260	TNFRSF1A	tumor necrosis factor receptor superfamily, member 1A	Yes
261	TP53	tumor protein p53 (Li-Fraumeni syndrome)	Yes
262	TRAF2	TNF receptor-associated factor 2	Yes
263	TRAF6	TNF receptor-associated factor 6	No
264	ZAK	-	No