

Table S1 Subject characteristics

Subject number	Extreme case/extreme control	Age	Packs-year	Sex	Stage	KRAS status
1	Case	34	23.5	Female	IV	Positive
2	Case	37	6	Male	IV	Unknown
3	Case	41	20	Female	IV	Unknown
4	Case	44	30	Female	IV	Unknown
5	Case	44	28	Female	IV	Positive
6	Case	45	30	Female	IV	Positive
7	Case	45	30	Male	IV	Unknown
8	Case	45	30	Female	IIB	Unknown
9	Case	45	25	Female	IV	Unknown
10	Case	45	15	Female	IV	Positive
11	Case	46	33	Male	IV	Unknown
12	Case	47	31	Male	III	Unknown
13	Case	48	30	Male	IV	Positive
14	Case	48	30	Male	IV	Unknown
15	Case	48	19	Male	IV	Negative
16	Case	49	64	Male	IV	Unknown
17	Case	49	60	Female	IIIA	Positive
18	Case	49	34	Male	IV	Unknown
19	Case	50	70	Male	IV	Unknown
20	Case	50	50	Male	IV	Unknown
21	Case	50	36	Male	IV	Unknown
22	Case	51	50	Male	IV	Positive
23	Case	51	39	Female	IV	Positive
24	Case	51	35	Male	IV	Negative
25	Case	51	30	Male	IV	Unknown
26	Case	51	30	Male	IV	Negative
27	Case	51	28	Female	I	Negative
28	Case	51	26	Male	I	Unknown
29	Case	51	17	Male	IV	Negative
30	Case	52	70	Male	IV	Unknown
31	Case	52	60	Male	IV	Negative
32	Case	52	60	Female	IV	Negative
33	Case	52	58.5	Female	IV	Negative
34	Case	52	50	Male	I	Positive
35	Case	52	30	Male	IV	Unknown
36	Case	53	66	Male	IV	Negative
37	Case	53	57	Male	IIIB	Negative
38	Case	53	53	Male	IV	Unknown
39	Case	53	37	Female	IV	Unknown
40	Case	53	32	Female	IV	Negative
41	Case	53	25	Male	IV	Positive
42	Case	54	129.5	Female	IIIB	Unknown
43	Case	54	90	Male	IV	Positive
44	Case	54	62.5	Male	IIIA	Positive
45	Case	54	37	Female	IV	Negative
46	Case	54	32	Male	III	Negative
47	Case	54	30	Female	IV	Positive
48	Case	55	99	Male	I	Unknown
49	Case	55	78	Male	IIIB	Negative
50	Case	55	72	Male	IIIB	Positive
Mean/distribution (%)		49.72	43.56	Female: 36%; male: 64%	I-II: 10%; II: 16%; IV: 74%	Positive: 28%; Negative: 28%; Unknown: 44%
1	Control	90	36	Male		
2	Control	85	30	Male		
3	Control	84	32	Male		
4	Control	83	52	Male		
5	Control	82	53	Male		
6	Control	82	120	Male		
7	Control	82	37.8	Male		
8	Control	81	50	Male		
9	Control	81	150	Male		
10	Control	80	51	Male		
11	Control	80	65	Male		
12	Control	80	107.5	Male		
13	Control	79	40	Male		
14	Control	79	70	Male		
15	Control	79	104	Male		
16	Control	79	79.5	Male		
17	Control	78	75	Male		
18	Control	78	60	Male		
19	Control	78	33	Male		
20	Control	78	28.5	Male		
21	Control	78	40	Male		
22	Control	78	50	Male		
23	Control	78	57	Male		
24	Control	77	60	Male		
25	Control	77	30	Female		
26	Control	77	22.2	Male		
27	Control	77	29.1	Male		
28	Control	77	68	Male		
29	Control	76	92.5	Male		
30	Control	76	50	Male		
31	Control	76	32	Male		
32	Control	76	22.5	Female		
33	Control	76	20	Female		
34	Control	75	54	Male		
35	Control	75	50	Female		
36	Control	75	40	Male		
37	Control	75	39	Male		
38	Control	75	20	Male		
39	Control	74	123.8	Male		
40	Control	74	60	Male		
41	Control	74	53	Male		
42	Control	74	52.1	Male		
43	Control	74	45	Male		
44	Control	74	27.5	Male		
45	Control	74	24	Male		
46	Control	74	23	Male		
47	Control	73	60	Male		
48	Control	73	100	Male		
49	Control	73	115.5	Male		
50	Control	72	105	Male		
Mean distribution (%)		77.5	56.79	Female: 8%; Male: 92%		

Table S2 Genes harboring several identified variants

Gene	Hits	Gene-adjusted P value
<i>PRAMEF2</i>	11	1.20E-12
<i>GBP4</i>	8	1.97E-06
<i>ANKRD36C</i>	7	2.28E-14
<i>PRAMEF19</i>	6	1.42E-07
<i>RP1L1</i>	6	0.000146459
<i>TTN</i>	6	2.74E-06
<i>APOL4</i>	5	4.36E-05
<i>RFPL2</i>	5	6.11E-05
<i>ZNF717</i>	5	5.36E-05
<i>ANKRD62</i>	4	1.44E-07
<i>HLA-A</i>	4	6.01E-06
<i>MUC3A</i>	4	0.002443697
<i>SLC22A20</i>	4	3.79E-05
<i>ALPK2</i>	3	3.83E-06
<i>CRIPAK</i>	3	2.21E-05
<i>EPB41L4A</i>	3	0.000948708
<i>FYCO1</i>	3	0.000358811
<i>HNRNPCL1</i>	3	1.25E-05
<i>HSPG2</i>	3	0.001280069
<i>ISCU</i>	3	0.00016821
<i>KCNK15</i>	3	0.000981465
<i>OR51A2</i>	3	0.000588876
<i>SAMD9</i>	3	9.88E-05
<i>ADAMTS13</i>	2	NA
<i>ADAMTS7</i>	2	NA
<i>AFAP1L2</i>	2	NA
<i>ALPK3</i>	2	NA
<i>ANKRD36</i>	2	NA
<i>C10orf113</i>	2	NA
<i>C2CD6</i>	2	NA
<i>C7orf31</i>	2	NA
<i>CACNA1A</i>	2	NA
<i>CCDC65</i>	2	NA
<i>CELSR1</i>	2	NA
<i>CRELD2</i>	2	NA
<i>CROCC</i>	2	NA
<i>CRYBG3</i>	2	NA
<i>DNAH17</i>	2	NA
<i>FAM71A</i>	2	NA
<i>FAM83B</i>	2	NA
<i>FCGBP</i>	2	NA
<i>FHL5</i>	2	NA
<i>FMN1</i>	2	NA
<i>FTSJ3</i>	2	NA
<i>FUT3</i>	2	NA
<i>ICE1</i>	2	NA
<i>KANK4</i>	2	NA
<i>KIAA1161</i>	2	NA
<i>KIF24</i>	2	NA
<i>KRT27</i>	2	NA
<i>KRT76</i>	2	NA
<i>MAGEC1</i>	2	NA
<i>NOC3L</i>	2	NA
<i>NWD1</i>	2	NA
<i>OR1B1</i>	2	NA
<i>OR1S1</i>	2	NA
<i>OR2M2</i>	2	NA
<i>OR52B6</i>	2	NA
<i>OR7G1</i>	2	NA
<i>PARP4</i>	2	NA
<i>PERM1</i>	2	NA
<i>PLIN4</i>	2	NA
<i>RBBP8NL</i>	2	NA
<i>REXO4</i>	2	NA
<i>RNF212</i>	2	NA
<i>RNF223</i>	2	NA
<i>RTN3</i>	2	NA
<i>SCN1B</i>	2	NA
<i>SHROOM3</i>	2	NA
<i>SLC14A1</i>	2	NA
<i>SLC26A8</i>	2	NA
<i>SPATA31E1</i>	2	NA
<i>SPINK5</i>	2	NA
<i>STEAP2</i>	2	NA
<i>STKLD1</i>	2	NA
<i>SUCLG2</i>	2	NA
<i>TCP10</i>	2	NA
<i>UBAP2</i>	2	NA
<i>VWA3A</i>	2	NA
<i>ZNF214</i>	2	NA
<i>ZNF761</i>	2	NA

Table S4 Genes harboring several validated variants

Gene	Hits
<i>PRAMEF19</i>	6
<i>RFPL2</i>	5
<i>PRAMEF2</i>	3
<i>HNRNPCL1</i>	2
<i>RP1L1</i>	2
<i>SAMD9</i>	2
<i>SHROOM3</i>	2
<i>STEAP2</i>	2
<i>ZNF717</i>	2
<i>ZNF761</i>	2