

## SUPPLEMENTARY INFORMATION

APPENDIX 1: List of analysed polymorphisms. Those marked with an asterisk have been previously reported on in the British sample (18, 50)

1. *AGTR1* (rs5188, rs2638359, rs5183, rs4681443, rs718858, rs389566)
2. *AKT1* (rs2498804, rs4983387, rs3803304, rs2494738, rs1130214)
3. *APAF1* (rs2278361, rs2288739, rs7965985, rs11109582)
4. *APC* (rs2229992, rs42427, rs2431509, rs1816769, rs2909962, rs454886, rs2545165, rs411356)
5. *ARHGDI1* (rs2075267, rs3983696, rs4703, rs1468890, rs10772826, rs2445433)
6. *ARTN* (rs2242637\*, rs6801, rs1859727)
7. *ATM* (rs172896, rs599164, rs637064, rs1263936, rs1801516)
8. *BAX* (rs1009316, rs2387583)
9. *BCL2* (rs4987872, rs1564483, rs1801018, rs1982673, rs4987825, rs899968, rs1545812, rs4987802, rs744569, rs2062011, rs2156193, rs4987768, rs1383596, rs1944419, rs4987736, rs1944420, rs2850763, rs1977971, rs1462129)
10. *BCL2L1* (rs6060563, rs2376996, rs6060599, rs6060812, rs1484994)
11. *BCR* (rs3761418, rs140504, rs2267009, rs2071433, rs1557496, rs2267019, rs928781, rs743584, rs131677)
12. *BRAF* (rs765373, rs2364399, rs3789806, rs1267622, rs1267621, rs1639675, rs1267606)
13. *CASP10* (rs3900115, rs12613347, rs3731714)
14. *CASP3* (rs1049253, rs6948, rs2705881, rs1405938, rs2720378)

15. *CASP8* (rs700635, rs6747918, rs1045485, rs3769827, rs3769825, rs3769821, rs2349070)
16. *CASP9* (rs1052576, rs4645983, rs2020900, rs951225, rs2020902)
17. *CCND3* (rs3218108, rs2479720, rs1051130, rs3218097)
18. *CD44* (rs17640, rs398734, rs1467558, rs2785172, rs353619, rs353612, rs353630, rs3794110, rs3736812, rs7930724, rs713330, rs2295756)
19. *CDC25A* (rs7617773, rs3731485, rs3731555, rs3731513, rs3731503)
20. *CDK2* (rs2069398, rs2069408)
21. *CDK4* (rs2069506, rs2270777)
22. *CDK6* (rs4272, rs42039, rs4380868, rs42046, rs2282979, rs3731343, rs2282985, rs3757823, rs10267477, rs2079147, rs4489250, rs3731314, rs3802076, rs1541380, rs8, rs3731288, rs992519, rs3731267)
23. *CDKN2A* (rs3731257, rs2518719, rs3731239, rs4074785, rs3731211, rs3731198, rs3731249)
24. *CDKN2B* (rs3217986, rs573687, rs643319, rs2069422, rs2069418, rs495490, rs2106119)
25. *CDKN2C* (rs1341980, rs12855, rs3176459)
26. *COMT* (rs165849, rs4633, rs933271, rs1544325, rs740603, rs740601, rs4646316)
27. *E2F1* (rs3213183, rs2071056, rs3213150)
28. *EGF* (rs10021697, rs718768, rs4444903, rs2237051, rs4698803, rs881878, rs3822288, rs7655579, rs2298983, rs3764861, rs2074390, rs10857004)
29. *EGFR* (rs1111650, rs1140475, rs2293347, rs763317, rs1015793, rs1024748, rs917879, rs984654, rs759169, rs4947971, rs2877260, rs6593206, rs4947979, rs6964705, rs2075110, rs759162, rs845551, rs845552, rs6970262)
30. *ERBB2* (rs1801200, rs1058808, rs2952155, rs1810132, rs4252627)

31. *FOS* (rs4645867, rs1569328, rs7101, rs1046117, rs4645856)
32. *GDNF* (rs11111\*, rs2910702, rs1981844, rs1862573, rs2975100)
33. *GFR $\alpha$ -1* (rs8192662, rs2420255, rs2245020\*, rs953920)
34. *GFR $\alpha$ -3* (rs7706366, rs7726580, rs10952\*)
35. *GRB2* (rs7219, rs1369299, rs4350602, rs9302990, rs4788891, rs1109033, rs959260)
36. *HIF1A* (rs12435848, rs2057482, rs2301106, rs1951795, rs2301111)
37. *HRAS* (rs12577324, rs8176332, rs4963176)
38. *IL2* (rs3136534, rs4833248, rs2069762)
39. *IL6* (rs2069849, rs2069832)
40. *MAP2K1* (rs1432443, rs4075493)
41. *MAP2K3* (rs1809238, rs3760201, rs2305871)
42. *MAP2K4* (rs1870584, rs8067785, rs2322123, rs9303045, rs7210799, rs2159140, rs1034870, rs757594, rs8082104, rs1870583)
43. *MAP2K6* (rs1989854, rs2072073, rs2715819, rs2716213, rs2251862, rs2715824, rs2716197, rs756944)
44. *MAPK14* (rs916346, rs3804451, rs3761980, rs851023, rs851019, rs851016, rs851010, rs851007, rs2815806)
45. *MAPKAPK2* (rs4590674, rs4845130, rs6691678, rs4240847)
46. *MAPKAPK5* (rs3741998, rs3213628, rs6489817, rs4767078, rs876896, rs9739377, rs1981517)
47. *MDM2* (rs937282, rs3730654, rs937283, rs3730646)
48. *NFK $\beta$*  (rs997476, rs980455, rs3774933, rs1598857, rs93059, rs230509, rs230498, rs1801, rs1020760, rs4235406, rs4648110)
49. *NFKB2* (rs7897947, rs11574849, rs7077329)
50. *NFKBIA* (rs3138056, rs3138052, rs3138043, rs2233419)

51. *NRTN* (rs1379868\*, rs778813)
52. *PCNA* (rs3730447, rs17352, rs17349)
53. *PIK3CB* (rs635592, rs361072, rs361071, rs361088, rs2595932, rs693293, rs361084, rs361061, rs500687)
54. *PIK3RI* (rs12755, rs3756668, rs40419, rs706713, rs7713645, rs251406, rs173702, rs10940159, rs706716, rs1819987, rs251409, rs1550805)
55. *PIK3R2* (rs273265, rs1011320, rs22679229)
56. *PTEN* (rs478839, rs1234221, rs1903858, rs2299939, rs1234213, rs2735343, rs926091)
57. *PTTG1* (rs2961952, rs1579074, rs3811999, rs4921281)
58. *RBI* (rs9568029, rs2804094, rs4151441, rs520342, rs4151474, rs399413, rs9568036, rs1894255, rs1951775, rs198575, rs198580, rs198590, rs367438)
59. *RELA* (rs11820062, rs7101916, rs7119750, rs11568300,)
60. *SOS1* (rs2888586, rs2060988, rs963828)
61. *STAT1* (rs6751855, rs1914408, rs1547550, rs10173099)
62. *STK6* (rs1044377, rs911160, rs6014711, rs1468056)
63. *TERT* (rs2853690, rs2075786)
64. *TNFRSF6* (rs7095466, rs3758483, rs2234978, rs2182408, rs9658727, rs982764)
65. *TNFSF6* (rs1492907, rs2859242, rs929087)
66. *TRAF1* (rs2239657, rs2416805)
67. *TRAF6* (rs1046864, rs331455, rs331457)
68. *VEGF* (rs998584, rs1547651, rs833060, rs699947, rs833068, rs3025010, rs3025035)
69. *WRN* (rs919002, rs2725349, rs1800391, rs1800392, rs2725362, rs1801196, rs7016874, rs2247189, rs2737327, rs3213202, rs6982004)

TABLES

**Table 1:** *STAT1* haplotype distributions for the Spanish, British, and pooled samples. H Freq: global frequency of haplotypes; H Freq 0: haplotype frequency in controls; H Freq 1: haplotype frequency in sMTC cases; OR: odds ratio. Haplotypes are constituted by 1914408, rs1547550, and rs10173099, with alleles presented in that order. Only haplotypes with an estimated frequency greater than 1% are shown. Green boxes indicate significant findings and brown boxes show not-significant findings containing the T allele for rs10173099.

	Spanish sample					British sample					Pooled sample				
	H Freq	H Freq 0	H Freq 1	OR	p-value	H Freq	H Freq 0	H Freq 1	OR	p-value	H Freq	H Freq 0	H Freq 1	OR	p-value
GGC	54.70%	55.90%	52.82%	0.88	0.252	52.96%	54.38%	50.16%	0.89	0.338	53.75%	54.64%	51.87%	0.89	0.172
AC [T]	15.27%	13.43%	19.13%	1.52	0.081	17.33%	16.98%	17.29%	1.02	0.702	16.36%	15.75%	18.08%	1.18	0.339
GG [T]	11.33%	9.64%	14.07%	1.54	0.012	10.84%	10.60%	11.42%	1.09	0.479	11.08%	10.23%	12.87%	1.30	0.021
ACC	7.61%	10.73%	1.49%	0.13	<0.001	5.77%	6.31%	4.26%	0.66	0.215	6.64%	8.25%	2.71%	0.31	0.000
GCC	6.73%	6.49%	7.45%	1.16	0.802	7.33%	7.46%	6.84%	0.91	0.709	7.05%	7.04%	7.21%	1.03	0.877
GC [T]	2.86%	2.45%	3.30%	1.36	0.205	3.68%	3.22%	5.06%	1.60	0.266	3.30%	2.90%	4.05%	1.42	0.119

**Table 2:** *AURKA* haplotype distribution for the Spanish, British, and pooled populations. H Freq: global frequency of haplotypes; H Freq 0: haplotype frequency in controls; H Freq 1: haplotype frequency in sMTC cases; OR: odds ratio. Haplotypes are constituted by rs1044377, rs911160, rs6014711, and rs1468056 with alleles presented in that order. Only haplotypes with an estimated frequency greater than 1% are shown. Green and yellow boxes indicate significant and marginal findings, respectively. Brown boxes show not-significant findings containing the C allele for rs911160.

	Spanish sample					British sample					Pooled sample				
	H Freq	H Freq 0	H Freq 1	OR	p-value	H Freq	H Freq 0	H Freq 1	OR	p-value	H Freq	H Freq 0	H Freq 1	OR	p-value
GGGG	32.44%	34.31%	29.60%	0.80	0.142	35.16%	37.15%	27.47%	0.64	0.001	33.92%	36.27%	28.88%	0.71	3.00E-04
GGGC	17.99%	18.91%	16.53%	0.85	0.210	16.50%	18.03%	12.29%	0.64	0.035	17.11%	18.04%	15.11%	0.81	0.05381
T [C] GG	15.92%	14.44%	17.82%	1.28	0.096	14.89%	14.30%	16.99%	1.23	0.091	15.29%	14.20%	17.44%	1.28	0.01222
GGAG	7.24%	6.82%	8.09%	1.20	0.336	11.47%	11.10%	12.72%	1.17	0.431	9.35%	9.17%	9.70%	1.06	0.60328
GGAC	6.31%	5.51%	7.49%	1.39	0.462	5.81%	5.50%	6.63%	1.22	0.383	6.03%	5.55%	7.14%	1.31	0.31503
T [C] GC	4.24%	4.18%	4.63%	1.11	0.673	2.57%	2.14%	3.80%	1.81	0.048	3.55%	3.22%	4.46%	1.40	0.08309
TGGG	3.90%	2.95%	5.27%	1.83	0.177	2.66%	2.77%	2.78%	1.00	0.930	3.34%	2.84%	4.43%	1.59	0.15119
G [C] GG	3.50%	3.34%	4.12%	1.24	0.357	4.32%	3.53%	7.37%	2.18	0.005	3.85%	3.34%	5.18%	1.58	0.02087
TGGC	2.70%	2.65%	2.84%	1.07	0.951	2.79%	2.31%	4.18%	1.85	0.194	2.71%	2.43%	3.30%	1.37	0.36038
G [C] GC	2.49%	2.37%	2.41%	1.02	0.670	1.32%	0.93%	2.14%	2.32	0.003	1.96%	1.71%	2.24%	1.31	0.06807
TGAC	2.31%	3.68%	0.28%	0.07	0.004	1.22%	1.08%	1.62%	1.51	0.144	1.83%	2.35%	0.70%	0.29	0.12649
TGAG	-	-	-	-	-	1.29%	1.07%	2.02%	1.91	0.112	-	-	-	-	-

**Table 3:** *CDKN2B* haplotype distribution for the Spanish dataset. H Freq: global frequency of haplotypes; H Freq 0: haplotype frequency in controls; H Freq 1: haplotype frequency in sMTC cases; OR: odds ratio. Haplotypes are constituted by rs2069418, rs573687, rs2106119, and rs643319, with alleles presented in that order. Only haplotypes with an estimated frequency greater than 1% are shown. Green and yellow boxes indicate significant and marginal findings, respectively.

	Spanish sample				
	H Freq	H Freq 0	H Freq 1	OR	p-value
GCCG	50.41%	46.02%	55.86%	1.48	0.010
CTTT	29.89%	32.84%	26.24%	0.73	0.058
GCTT	11.70%	12.19%	11.10%	0.90	0.636
CCTG	6.47%	7.96%	4.62%	0.56	0.067
GCTG	1.11%	0.75%	1.56%	2.10	0.306

**Table 4:** *BCL2* haplotype distribution for the Spanish population. H Freq: global frequency of haplotypes; H Freq 0: haplotype frequency in controls; H Freq 1: haplotype frequency in sMTC cases; OR: odds ratio. Haplotypes are constituted by 1462129 and rs1801018, with alleles presented in that order. Only haplotypes with an estimated frequency greater than 1% are shown. Green boxes define significant findings.

	Spanish sample				
	H Freq 0	H Freq 1	OR	H Score	p-value
CG	37.11%	52.60%	1.88	4.375	<0.001
TA	47.23%	35.54%	0.62	-3.498	<0.001
CA	14.27%	11.51%	0.78	-1.149	0.251

**Table 5:** *HRAS* haplotype distribution for the Spanish population. H Freq: global frequency of haplotypes; H Freq 0: haplotype frequency in controls; H Freq 1: haplotype frequency in sMTC cases; OR: odds ratio. rs12577324 and rs8176332 are the genetic variants that constitute these haplotypes, and only those with a frequency greater than 1% are shown. Green boxes define significant findings.

	Spanish sample				
	H Freq	H Freq 0	H Freq 1	OR	p-value
TC	80.76%	81.30%	79.86%	0.91	0.536
CA	11.86%	10.11%	14.71%	1.53	0.022
CC	7.39%	8.59%	5.43%	0.61	0.045