SUPPLEMENTARY MATERIAL

Supplementary Methods

Clinicopathological and demographic variables associated with overall survival in our patient population (Supplementary Table 4)

In order to assess which clinicopathological and demographic variables impact overall survival in our patient set, we tested each of these variables in separate univariate Cox proportional hazards models. As can be seen in Supplementary Table 4, stage, primary tumor thickness, ulceration, mitotic rate, histological subtype, and age at diagnosis were all strongly associated with overall survival. In addition, family history, AJ ancestry, and gender showed borderline associations. We then incorporated each of these variables into a single multivariate model in order to identify which were independently associated with survival (Supplementary Table 4). While the strength of each association was reduced, likely due to the correlations between some clinicopathological variables as well as their inclusion into the staging system, many remained significant (*P* value <0.05): stage, thickness, ulceration, histological subtype, and age at diagnosis. Mitotic rate, family history of melanoma and gender were not significant prognostic factors when included into this multivariate model.

Survival analysis of *IL10* haplotypes. (Supplementary Table 5)

Haplotype blocks were defined for SNPs associated with melanoma overall survival (*P* value <0.05) in the fine mapping analysis of the 1q32.1 locus (Haploview). Haplotypes were phased using plink, and haplotypes with the highest probability for each individual were included into a

multivariate Cox proportional hazards model to assess their correlation with melanoma overall survival.

Supplementary Table 1: Previous reports on association between genetic variation in immunomodulatory genes and cutaneous melanoma survival

Immunomodulatory genetic variants discovered	Cohort size	No. of immunomodulatory genes analysed	No. of SNPs analysed	Outcome	Reference
CD28 rs3181098	763	3	25	reduced metastases free survival (P=0.06)	[1]
HLA-DBQ1*0301	259		1	decreased disease-free survival (P=0.0002)	[2]
ICOS rs11571323	763	3	25	with reduced overall survival (P=0.04)	[1]
IFNG rs2430561	90	2	2	reduced overall survival (P<0.001)<	[3]
IFNW1 rs10964859	752	15	44	reduced overall survival (P=0.04); increased risk of death following metastasis (P=0.01)	[4]
IFNW1 rs10964862	752	15	44	reduced melanoma-free survival (P=0.04); increased risk of death following metastasis (P=0.04)	[4]
IL10 rs1518111	552	9	35	increased risk for melanoma-related mortality (P=0.026)	[5]
IL10 rs18000871	42	3	5	decreases survival time (P=0.05)	[6]
IL10 rs18000896	98	1	3	decreased survival time and mean age at diagnosis (P<0.05)	[7]
IL10 rs18000896	42	3	5	decreases survival time (P=0.002)	[6]
IL10 rs18000896	90	2	2	reduced overall survival (P=0.065)	[3]
IL10 rs1800871	552	9	35	increased risk for melanoma-related mortality (P=0.018)	[5]
IL10 rs1800872	552	9	35	increased risk for melanoma-related mortality (P=0.025)	[5]
TLR3 rs13126816	552	9	35	increased risk for melanoma-related mortality (P=0.014)	[5]
TLR3 rs3775291	552	9	35	increased risk for melanoma-related mortality (P=0.04)	[5]

References

1. Bouwhuis MG, Gast A, Figl A, Eggermont AM, Hemminki K, Schadendorf D, Kumar R. Polymorphisms in the CD28/CTLA4/ICOS genes: role in malignant melanoma susceptibility and prognosis? Cancer immunology, immunotherapy : CII 2010;**59**(2):303-12 doi: 10.1007/s00262-009-0751-2[published Online First: Epub Date]|.

2. Lee JE, Lu M, Mansfield PF, Platsoucas CD, Reveille JD, Ross MI. Malignant melanoma: relationship of the human leukocyte antigen class II gene DQB1*0301 to disease recurrence in American Joint Committee on Cancer Stage I or II. Cancer 1996;**78**(4):758-63 doi: 10.1002/(SICI)1097-0142(19960815)78:4<758::AID-CNCR11>3.0.CO;2-U[published Online First: Epub Date]|.
3. Liu D, O'Day SJ, Yang D, Boasberg P, Milford R, Kristedja T, Groshen S, Weber J. Impact of gene polymorphisms on clinical outcome for stage IV melanoma patients treated with biochemotherapy: an exploratory study. Clin Cancer Res 2005;**11**(3):1237-46
4. Lenci RE, Bevier M, Brandt A, Bermejo JL, Sucker A, Moll I, Planelles D, Requena C, Nagore E, Hemminki K, Schadendorf D, Kumar R. Influence of genetic variants in type I interferon genes on melanoma survival and therapy. PloS one 2012;**7**(11):e50692 doi: 10.1371/journal.pone.0050692[published Online First: Epub Date]|.
5. Park JY, Amankwah EK, Anic GM, Lin HY, Walls B, Park H, Krebs K, Madden M, Maddox K, Marzban S, Fang S, Chen W, Lee JE, Wei Q, Amos CI, Messina JL, Sondak VK, Sellers TA, Egan KM. Gene variants in angiogenesis and lymphangiogenesis and cutaneous melanoma progression. Cancer Epidemiol Biomarkers Prev 2013;**22**(5):827-34 doi: 10.1158/1055-9965.EPI-12-1129[published Online First: Epub Date]|.
6. Martinez-Escribano JA, Moya-Quiles MR, Muro M, Montes-Ares O, Hernandez-Caselles T, Frias JF, Alvarez-Lopez MR. Interleukin-10, interleukin-6 and interferon-gamma gene polymorphisms in melanoma patients. Melanoma Res 2002;**12**(5):465-9
7. Alonso R, Suarez A, Castro P, Lacave AJ, Gutierrez C. Influence of interleukin-10 genetic polymorphism on survival rates in melanoma patients with advanced disease. Melanoma Res 2005;**15**(1):53-60

Supplementary Table 2: List of 72 tag SNPs in 44 candidate immunomodulatory genes

SNP	Gene	Position (hg19)
rs12024371	BCL10	chr1:85738184
rs12744565	BCL10	chr1:85739777
rs7540530	RORC	chr1:151790857
rs3024493	IL10	chr1:206943967
rs3024490	IL10	chr1:206945310
rs2222202	IL10	chr1:206945380
rs12407485	IL19	chr1:206981718
rs12145973	IL19	chr1:206994724
rs2243193	IL19	chr1:207016224
rs1400986	IL20	chr1:207038685
rs2981573	IL20	chr1:207040576
rs1518108	IL20	chr1:207043173
rs1417488	TGFB2	chr1:218523729
rs2009112	TGFB2	chr1:218553528
rs10779329	TGFB2	chr1:218573740
rs2856836	IL1A	chr2:113532082
rs1609682	IL1A	chr2:113540204
rs1143634	IL1B	chr2:113590389
rs1143633	IL1B	chr2:113590466
rs2723168	IL37	chr2:113670889
rs3811047	IL37	chr2:113671409
rs12711747	IL36B	chr2:113785019
rs1562302	IL36B	chr2:113810457
rs231777	CTLA4	chr2:204733587
rs231779	CTLA4	chr2:204734486
rs2227543	IL8	chr4:74607909
rs2069772	IL2	chr4:123373132
rs2221903	IL21	chr4:123538911
rs13143866	IL21	chr4:123540757
rs4956405	IL15	chr4:142627648
rs10519610	IL15	chr4:142637100
rs40401	IL3	chr5:131396477
rs2069812	IL5	chr5:131879915
rs848	IL13	chr5:131996499
rs2243266	IL4	chr5:132013788
rs1859430	IL9	chr5:135230512
rs2227447	IL17B	chr5:148758026
rs2069840	IL6	chr7:22768571
rs6993386	IL7	chr8:79654144

rs12551256	IL33	chr9:6231238
rs3781092	GATA3	chr10:8106352
rs3882891	IL18	chr11:112014760
rs11570948	IL26	chr12:68603962
rs2046068	IL22	chr12:68645974
rs17224704	IL22	chr12:68646835
rs7977932	IL31	chr12:122657382
rs6490605	IL17D	chr13:21285008
rs6783	IL17D	chr13:21297049
rs7145531	IL25	chr14:23842016
rs3811178	IL25	chr14:23845243
rs1009978	LGALS3	chr14:55603060
rs11639206	IL16	chr15:81498927
rs4573895	IL16	chr15:81499153
rs12441273	IL16	chr15:81519580
rs4778888	IL16	chr15:81524612
rs4072680	IL16	chr15:81584388
rs1554999	IL32	chr16:3115627
rs11865804	IL34	chr16:70681490
rs305083	IRF8	chr16:85935877
rs2292980	IRF8	chr16:85945075
rs12926854	IRF8	chr16:85951257
rs16940005	IRF8	chr16:85953681
rs2107538	CCL5	chr17:34207779
rs2293154	STAT5A	chr17:40461002
rs2293152	STAT3	chr17:40481528
rs2306580	STAT3	chr17:40491679
rs11657479	TBX21	chr17:45822900
rs3093030	ICAM1	chr19:10397402
rs11888	JAK3	chr19:17935625
rs3212760	JAK3	chr19:17947545
rs1042506	IL11	chr19:55877110
rs10964859	IFNW1	chr9:21140672

Supplementary Table 3: List of 24 tag SNPs selected for fine mapping of the 1q32.1 locus.

SNP	Position (hg19)
rs6658896	chr1:206926845
rs6692511	chr1:206927515
rs4390174	chr1:206932450
rs13376708	chr1:206932502
rs3021094	chr1:206944951
rs3024491	chr1:206945045
rs1800871	chr1:206946633
rs1800894	chr1:206946665
rs1800896	chr1:206946896
rs1800890	chr1:206949364
rs4072227	chr1:206957557
rs6683473	chr1:206967151
rs10746433	chr1:206974966
rs12046559	chr1:206989066
rs1028182	chr1:207001878
rs2243188	chr1:207014471
rs960326	chr1:207014775
rs7528265	chr1:207019162
rs1033272	chr1:207030984
rs41434745	chr1:207031791
rs1109461	chr1:207041802
rs3024521	chr1:207042276
rs3093445	chr1:207073909
rs12121499	chr1:207080564

Supplementary Table 4: Association between clinical covariates and OS

		Univariate		Multivariate	
Variable	**No. (%)**	**HR (CI 95%)**	***P* value[1]**	**HR (CI 95%)**	***P* value[1]**
Stage at primary diagnosis					
I	803 (67.7)	Ref		Ref	
II	196 (16.5)	3.46 (2.31-5.21)		1.32 (0.65-2.67)	
III	187 (15.8)	5.10 (3.51-7.42)	$<2.2x10^{-16}$	2.90 (1.48-5.69)	0.00012
Primary tumor thickness					
<1.0	609 (52.7)	Ref		Ref	
1.0-2.0	265 (22.9)	1.53 (0.93-2.51)		1.20 (0.64-2.25)	
2.01-4.0	168 (14.5)	3.18 (2.00-5.04)		1.12 (0.51-2.47)	
>4.0	113 (9.8)	6.56 (4.20-10.26)	$<2.2x10^{-16}$	2.21 (0.97-5.01)	0.025
Ulceration					
No	940 (81.8)	Ref		Ref	
Yes	209 (18.2)	3.64 (2.64-5.02)	$3.59x10^{-14}$	1.61 (1.06-2.44)	0.023
Mitotic rate					
<1/mm^2	647 (59.5)	Ref		Ref	
≥1/mm^2	441 (40.5)	2.49 (1.76-3.52)	$1.24x10^{-7}$	1.14 (0.72-1.79)	0.57
Primary tumor anatomic site					
Axial	655 (56.5)	Ref		-	
Extremity	504 (43.5)	0.81 (0.58-1.13)	0.20	-	-
Histological subtype					
Superficial Spreading	642 (59.2)	Ref		Ref	
Nodular	278 (25.6)	3.51 (2.41-5.13)		1.63 (1.01-2.64)	
Other	165 (15.2)	2.85 (1.78-4.58)	$2.36x10^{-11}$	2.24 (1.32-3.80)	0.011
Sentinel Lymph Node Biopsy					
No		Ref		-	
Yes		1.25 (0.91-1.72)	0.17	-	-
Age at primary diagnosis					
≤60	630 (53.1)	Ref		Ref	
>60	556 (46.9)	2.29 (1.67-3.16)	$2.31x10^{-7}$	1.96 (1.36-2.83)	0.00024
Gender					
Female	436 (42.6)	Ref		Ref	
Male	588 (57.4)	1.34 (0.97-1.86)	0.074	1.21 (0.84-1.74)	0.31
Family History of Melanoma					
No	948 (83.6)	Ref		Ref	
Yes	186 (16.4)	0.56 (0.34-0.92)	0.014	0.69 (0.39-1.23)	0.19

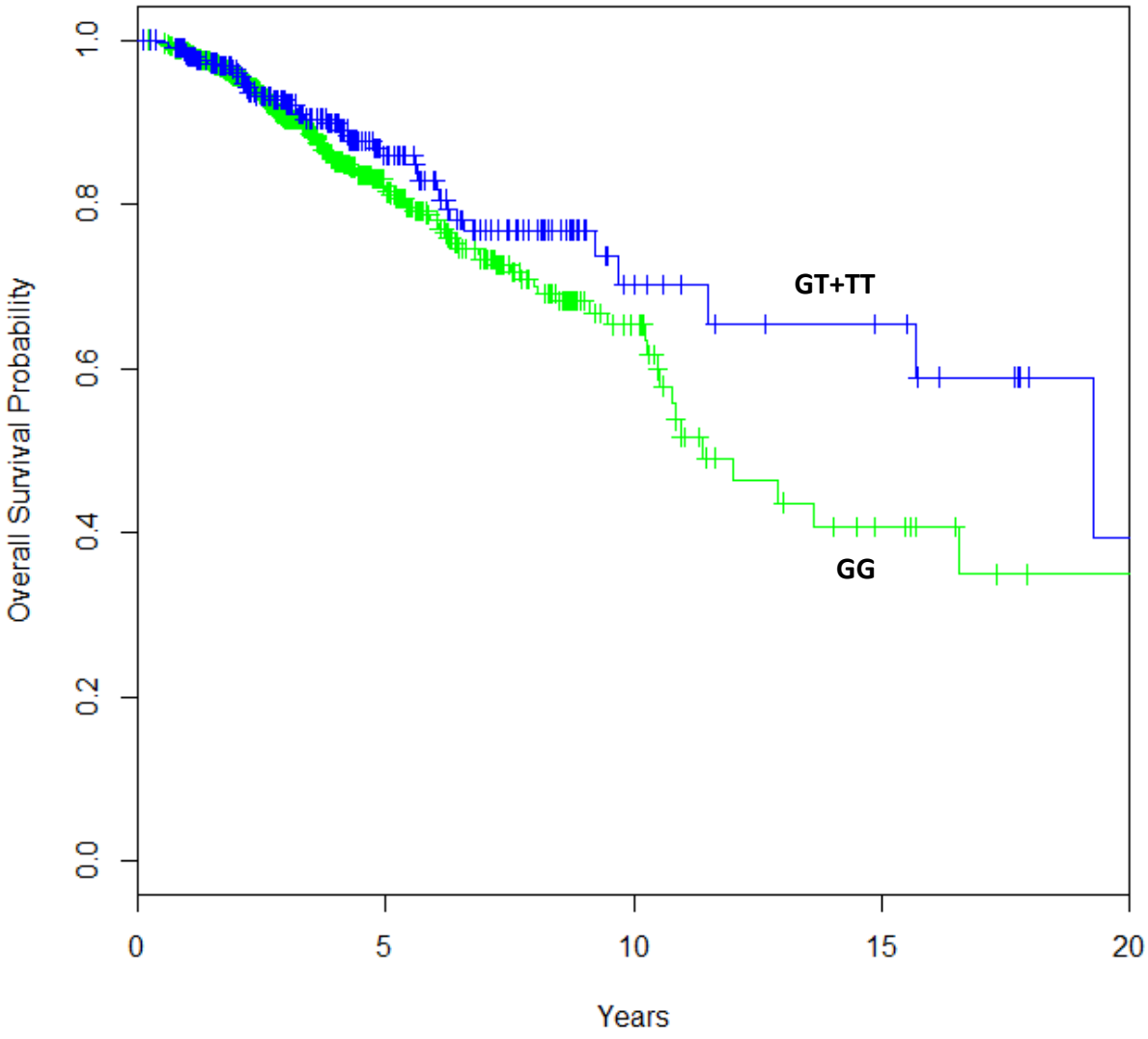
[1]*P* value based on likelihood ratio test.

Supplementary Table 5: IL10 haplotype analysis.

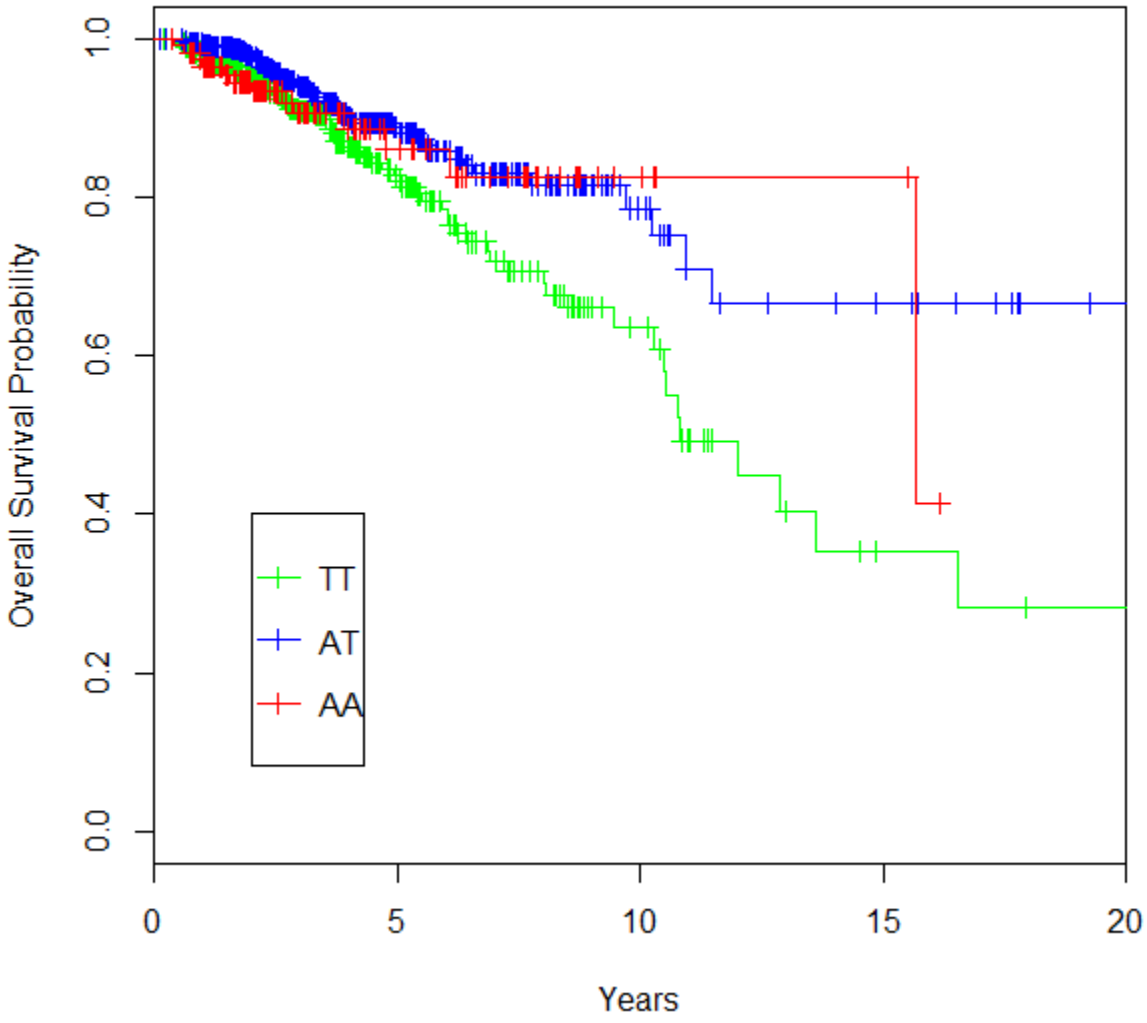
IL10 Haplotype	Count (Freq.)	HR (95% CI)	*P* value
GGCAT/GGCAT	270 (0.29)	Ref	Ref
GTTGA/GGCAT	206 (0.22)	0.47 (0.26-0.86)	0.013
TTTGA/GGCAT	158 (0.17)	0.42 (0.22-0.79)	0.0074
GTTGT/GGCAT	88 (0.09)	0.87 (0.46-1.62)	0.66
GTTGA/TTTGA	63 (0.07)	0.23 (0.08-0.66)	0.0061
TTTGA/GTTGT	40 (0.04)	0.41 (0.15-1.08)	0.07
GTTGA/GTTGA	39 (0.04)	0.4 (0.12-1.36)	0.14
GTTGT/GTTGA	37 (0.04)	1.03 (0.31-3.41)	0.96
TTTGA/TTTGA	17 (0.02)	4.68 (1.60-13.7)	0.0048
GTTGT/GTTGT	11 (0.01)	0.46 (0.06-3.46)	0.45
			0.00069*

**P* value based on omnibus haplotype block association test.

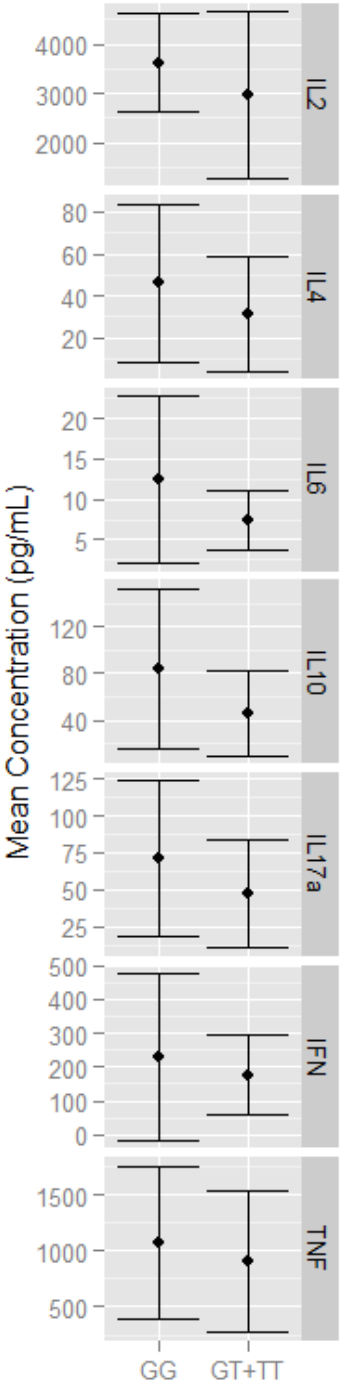
Supplementary Figure 1: Kaplan-Meier plot for rs3024493 genotypes associated with overall survival (*P* value = 0.027). *P* value was calculated using log-rank test.



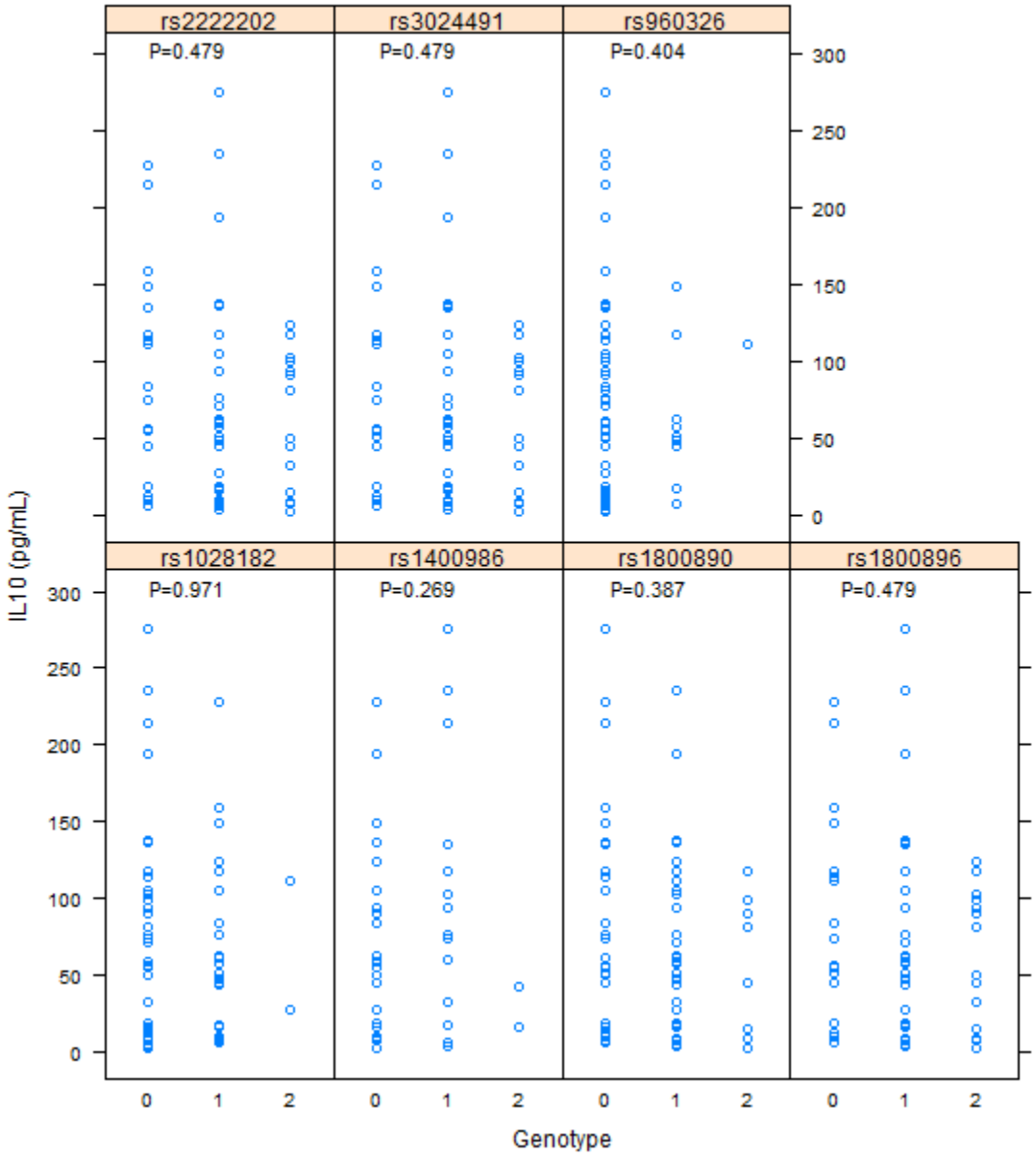
Supplementary Figure 2: Kaplan-Meier plot for rs1800890 genotypes associated with overall survival (*P* value = 0.0048) *P* value was calculated using log-rank test.



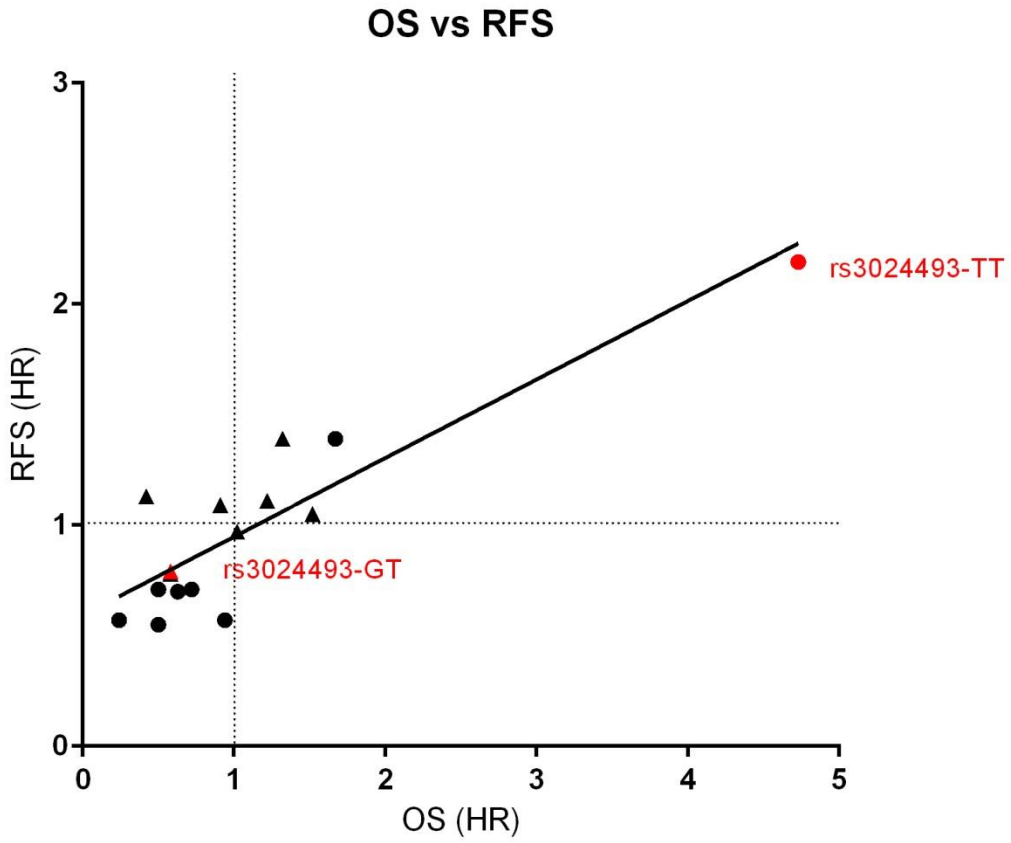
Supplementary Figure 3: Correlation between rs3024493 genotypes and secretion of seven selected cytokines



Supplementary Figure 4: Correlation between other 1p32 variants and IL10 secretion. Genotypes are marked with 0 – reference homozygotes; 1- heterozygotes and 2 – minor allele homozygotes. Spearman correlation test was used for assessing the statistical significance (*P* values).



Supplementary Figure 5: Overall survival versus recurrence-free survival by SNPs from Table2. Estimated hazard ratios (HR) of heterozygotes (▲) and minor allele homozygotes (●) for variants significantly associated in OS are plotted. Most significantly associated variant in the study is marked (*red*). Pearson's correlation was used to assess relationship between OS and RFS (r=0.89, P<0.0001).



Note that HR >1 indicates potential risk effect and HR<1 indicates protective effect. While overall concordance between the HRs of OS and RFS is clearly very high, the concordance is actually perfect among the minor allele homozygotes (●) as also summarized below:

	OS HR<1	OS HR>1
RFS HR<1	6	0
RFS HR>1	0	2