Supplementary Methods

Methods

SNP genotyping

In the discovery MDACC CM GWAS dataset, genomic DNA was extracted from CM patients for genotyping using the Illumina HumanOmni-Quad_v1_0_B array. The genotyping data are available from the National Center for Biotechnology Information Database of Genotypes and Phenotypes (dbGaP Study Accession: phs000187.v1.p1). Genome-wide imputation was performed based on the 1000 Genomes Project, phase I v2 CEU, utilizing the MACH software (March 2010 release). Following strict criteria (imputation info score ≥0.8, a genotyping rate ≥95%, a minor allelic frequency ≥5%, and Hardy-Weinberg equilibrium $\geq 1\times10^{-5}$), we extracted SNPs within ± 2 kilobase flanking regions of myeloid cell-related pathway genes from the MDACC CM GWAS dataset. For the NHS/HPFS replication datasets, genotyping of DNA samples was performed with the HumanHap610 array, the Affymetrix 6.0 array, and the Illumina HumanHap550 array. Further imputation was performed depending on haplotype information and genotyped SNPs from 1000 Genomes Project phase II CEU data by applying the MACH program (March 2012 release). The genotyping data were extracted from the NHS/HPFS CM GWAS datasets, following the same quality-control criteria for those from the MDACC CM GWAS dataset.

Statistical methods

For the present study, CMSS was defined as the period from the date of diagnosis of CM to the date of death from CM or the end of follow-up, whichever came first. CM patients known to be alive were censored at the time of the last contact. In the discovery MDACC dataset, we first assessed the associations between all available SNPs in 280 myeloid cell-related pathway genes and CMSS in a single-locus analysis using the GenABEL package of R software. Then multivariable Cox proportional hazards regression analyses were performed with adjustment for available covariates in the MDACC dataset (including age, sex, Breslow thickness, ulceration, distant/regional metastasis, and mitotic rate); however, in the replication NHS/HPFS dataset, the only variables covariates for adjustment were age and sex. In view of the high level of linkage disequilibrium among acquired SNPs, we employed Bayesian false discovery probability (BFDP) with a cutoff value of 0.80 for multiple testing correction to lower the probability of potentially false positive results. In addition, we assigned a prior probability of 0.10 and an upper boundary hazards ratio (HR) of 3.0 for an association with variant genotypes or minor alleles of the SNPs with $P<0.05$. Next, we applyed a multivariable stepwise Cox regression model to identify independent tag SNPs in the MDACC dataset that had more covariate information. We then adopted a meta-analysis to combine the results of the identified SNPs from the MDACC dataset and the NHS/HPFS dataset using PLINK 1.90 with the Cochran's Q statistics and I^2 for heterogeneity test. Because there was no significant heterogeneity between the MDACC dataset and the NHS/HPFS dataset (Q test $P > 0.1$, $I^2 < 25.0\%$), we performed the meta-analysis with a fixed-effects model. We subsequently evaluated the cumulative effects of all identified SNPs by adding up the risk alleles. For the stratified analyses by subgroups, we calculated inter-study heterogeneity and evaluated the interaction. To evaluate the correlation between the identified SNPs and their genes' mRNA expression, we employed expression quantitative trait loci analyses with a linear regression model using data from the 373 European descendants included in the 1,000 Genomes Project, the genotype-tissue expression project, and The Cancer Genome Atlas database using R software (version 3.5.0). Finally, we explored the association between the mRNA expression levels of the genes where the SNPs are located and CM survival using the KM analysis from an online database. All statistical analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC) unless specified otherwise.

Supplementary Table 1. List of 280 selected genes in the myeloid cell-related pathway

Dataset	Name of pathway	Number of genes
GO	GO_NEGATIVE_REGULATION_OF_MYELOID_CELL_DIFFERENTIATION	92
GO	GO_HEMATOPOIETIC_STEM_CELL_PROLIFERATION	23
GO	GO_HEMATOPOIETIC_PROGENITOR_CELL_DIFFERENTIATION	162
GO	GO_GRANULOCYTE_DIFFERENTIATION	33
REACTOME	REACTOME_RUNX1_REGULATES_TRANSCRIPTION_OF_GENES_INVOLVED_IN_DIFFERENTIATION_OF_MYELOID_CELLS_7	7
KEGG	-	0
BIOCARTA	-	0
PID	-	0
Total	*C1QC, HAX1, LBR, TAL1, ACP6, HES5, KCNAB2, MIXL1, PRRC2C, PSMA5, PSMB2, PSMB4, PSMD4, PTPRC, SSBP3, TP73, WDR78, YTHDF2, CD34, WNT2B, APCS, CDC73, HIST2H4A, HIST2H4B, ITPKB, PIAS3, RBM15, INPP5D, SP3, EIF2AK2, NFE2L2, PLEK, PSMD1, PSMD14, PSME4, SOS1, XRCC5, GPR55, INHA, MEIS1, TMEM178A, ADIPOQ, GATA2, HCLS1, JAGN1, DHX36, HES1, HYAL2, MLF1, PSMD2, PSMD6, TREX1, ARIH2, MECOM, THPO, WNT5A, CLDN18, CTNNB1, GPR171, LTF, TCTA, LEF1, HERC6, KIT, PDGFRA, RBM47, REST, SFRP2, FBXW7, PF4, TLR3, CSF2* *IL5, CSF1R, FNIP1, FST, PDGFRB, TENT2, CARTPT, HSPA9* *IL4, PIK3R1, L3MBTL3, BVES, DACT2, FOXC1, MYB, PDCD2, PSMB1, PSMB8, PSMB9, SOX4, SRF, ZBTB24, DLL1, HIST1H4A, HIST1H4B, HIST1H4C, HIST1H4D, HIST1H4E, HIST1H4F, HIST1H4H, HIST1H4I, HIST1H4J, HIST1H4K, HIST1H4L, RUNX2, ANLN, BRAF, CDK6, INHBA, PSMA2, PSMC2, PTPRZ1, PUS7, SHH, HOXA5, HOXA7, HOXA9, LRRC17, NCAPG2, TRIB1, AGPAT5, CEBPD, ESCO2, PRKDC, RRS1, SFRP1, ZFAT, LYN, MYC* *PTK2B, ABL1, NOTCH1, PSMB7, TLR4, DHTKD1, GATA3, LDB1, MMP21, SPI1, DPF2, JAM3, KMT2A, LMO1, LMO2, PSMA1, PSMC3, PSMD13, YAP1, CTR9, MIR125B1, UBASH3B, ZBTB16, TESC, C12orf29, KRT75, PSMD9, PTPN6, ETV6, KITLG, SART3* *WNT1, WNT10B, HIST4H4, CUL4A, ARHGEF7, ARL11, FLT3, LIG4, N4BP2L2, CEBPE, IL25, BATF, BMP4, EML1, METTL3, PLD4, PSEN1, PSMA3, PSMA6, PSMB11, PSMB5, PSMC1, PSMC6, PSME1, PSME2, SLC8A3, STON2, ZBTB1, GPR68, NFKBIA, ZFP36L1, LGALS3, PSMA4, PYGO1, SIN3A, TCF12, CIB1, FBN1, KLF13, LEO1, MEIS2, WDR61, CBFA2T3, ZFPM1, CBFB, CIAO3, NUDT21, PSMB10, PSMD7, SETD1A, SLC7A6OS, SMPD3, ATXN1L, CREBBP, PRKCB, CSF3, DHRS7B, EVI2B, FASN, RARA, ACE, FLCN, HEATR9, HOXB3, HOXB4, MEOX1, PSMB3, PSMB6, PSMC5, PSMD11, PSMD12, PSMD3, PSME3, TNFRSF13B, TOP2A, CTC1, CCL3, HOXB8, NF1, NME1, NME2, STAT5B, BCL2, PSMA8, SERPINB12, WDR7, PTPN2, CEACAM1, CEBPA, ARMC6, EEF2, ERCC2, FSTL3, PSMC4, PSMD8, SIPA1L3, TCF3, TGFB1, TMEM190, TMEM91, ZNF784, BABAM1, LILRB1, LILRB3, LILRB4, PAF1, PRMT1, ZFP36, ZNF675, ZBTB46, ITCH, PSMA7, PSMF1, MAFB, RUNX1, GABPA, MIR125B2, TOB2* (after removing the duplicated 31 genes, 5 genes in X chromosome, 1 pseudogenes)	280

Keyword: myeloid cell; Organism: Homo sapiens; Website: http://software.broadinstitute.org/gsea/msigdb/search.jsp.

Supplementary Table 2. Distributions of the characteristics of CM patients in the MDACC and Harvard genotyping datasets

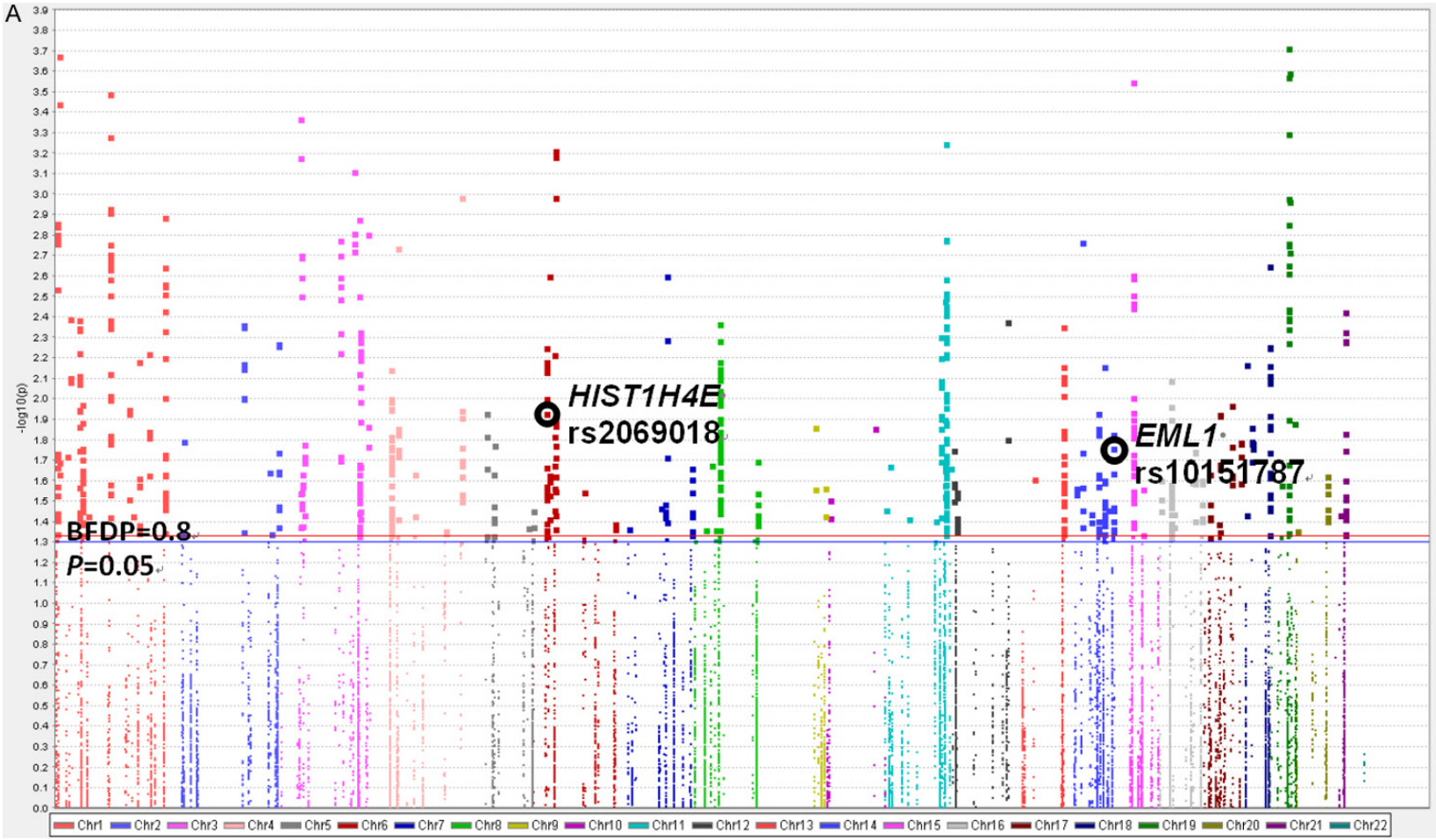
Parameter		Frequency		MFT	HR (95% CI)[a]	*P*[a]
		Patient	Death (%)			
MDACC		858	95 (11.1)	81.1		
Age (years)	≤50	371	31 (8.4)	85.8	1.00	
	>50	487	64 (13.1)	78.1	1.69 (1.10-2.59)	0.017
Sex	Female	362	26 (7.2)	85.9	1.00	
	Male	496	69 (13.9)	77.8	2.07 (1.32-3.25)	0.002
Regional/distant metastasis	No	709	51 (7.2)	82.7	1.00	
	Yes	149	44 (29.5)	69.4	4.78 (3.19-7.15)	<0.001
Breslow thickness (mm)	≤1	347	7 (2.0)	85.0	1.00	
	>1	511	88 (17.2)	78.1	9.17 (4.25-19.80)	<0.001
Ulceration	No	681	48 (7.1)	84.0	1.00	
	Yes	155	43 (27.7)	64.3	4.91 (3.29-7.42)	<0.001
	Missing	22				
Mitotic rate (mm^2)	≤1	275	9 (3.3)	82.2	1.00	
	>1	583	86 (14.8)	80.1	4.67 (2.35-9.29)	<0.001
Harvard		409	48 (11.5)	179.0		
Age (years)	≤50	72	3 (4.2)	352.5	1.00	
	>50	337	45 (13.4)	167.0	4.04 (1.25-13.06)	0.020
Sex	Female	271	31 (11.4)	198.0	1.00	
	Male	138	17 (12.3)	155.5	1.16 (0.64-2.10)	0.622

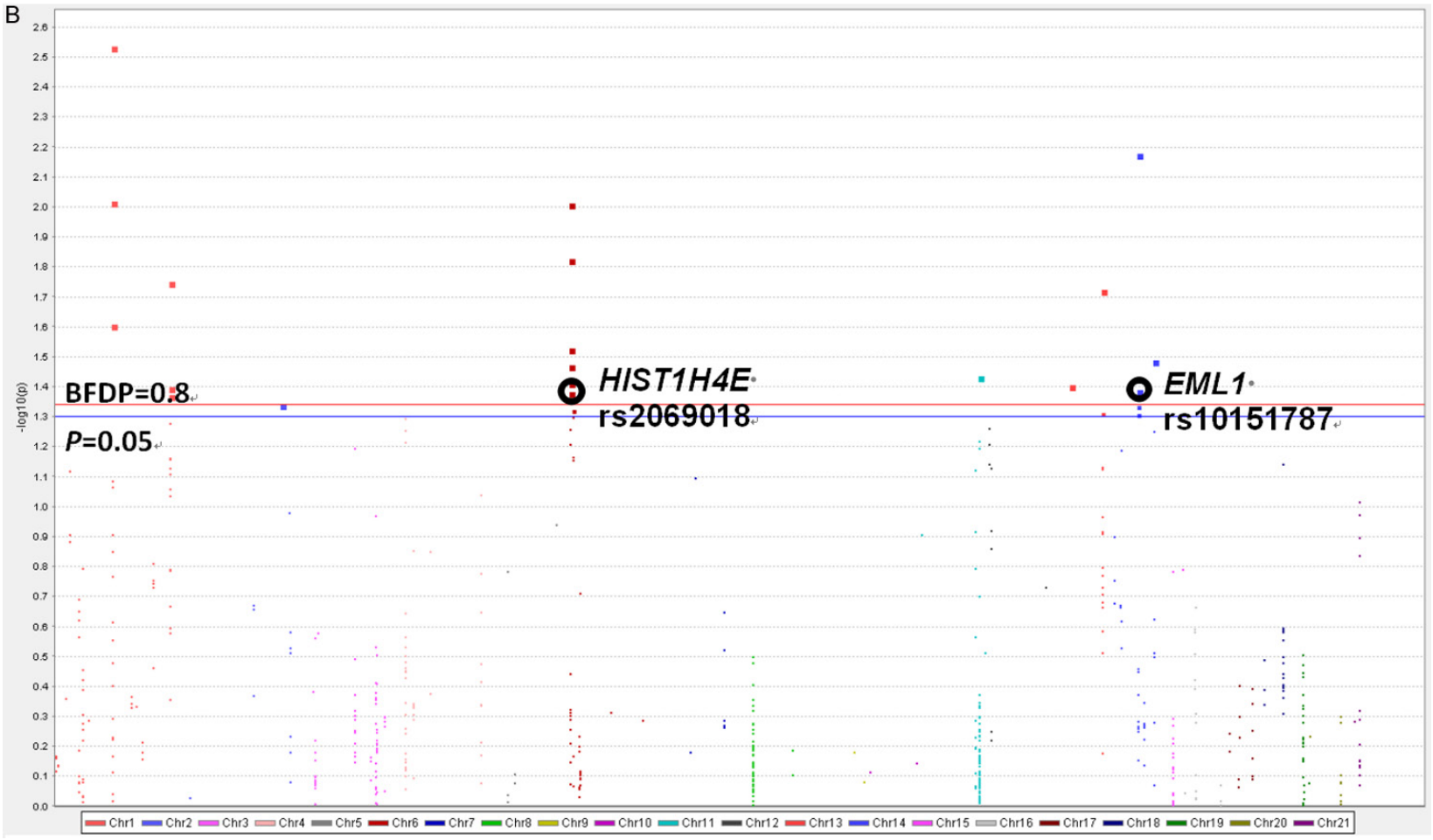
Abbreviations: CM, cutaneous melanoma; MDACC, The University of Texas MD Anderson Cancer Center; MFT, median follow-up time (months); HR, hazards ratio; CI, confidence interval. [a]Univariate Cox proportional hazards regression analysis.

Supplementary Table 3. Functional prediction of 22 validated SNPs in high linkage disequilibrium (LD) ($r^2 \geq 0.8$) in myeloid cell-related pathway genes

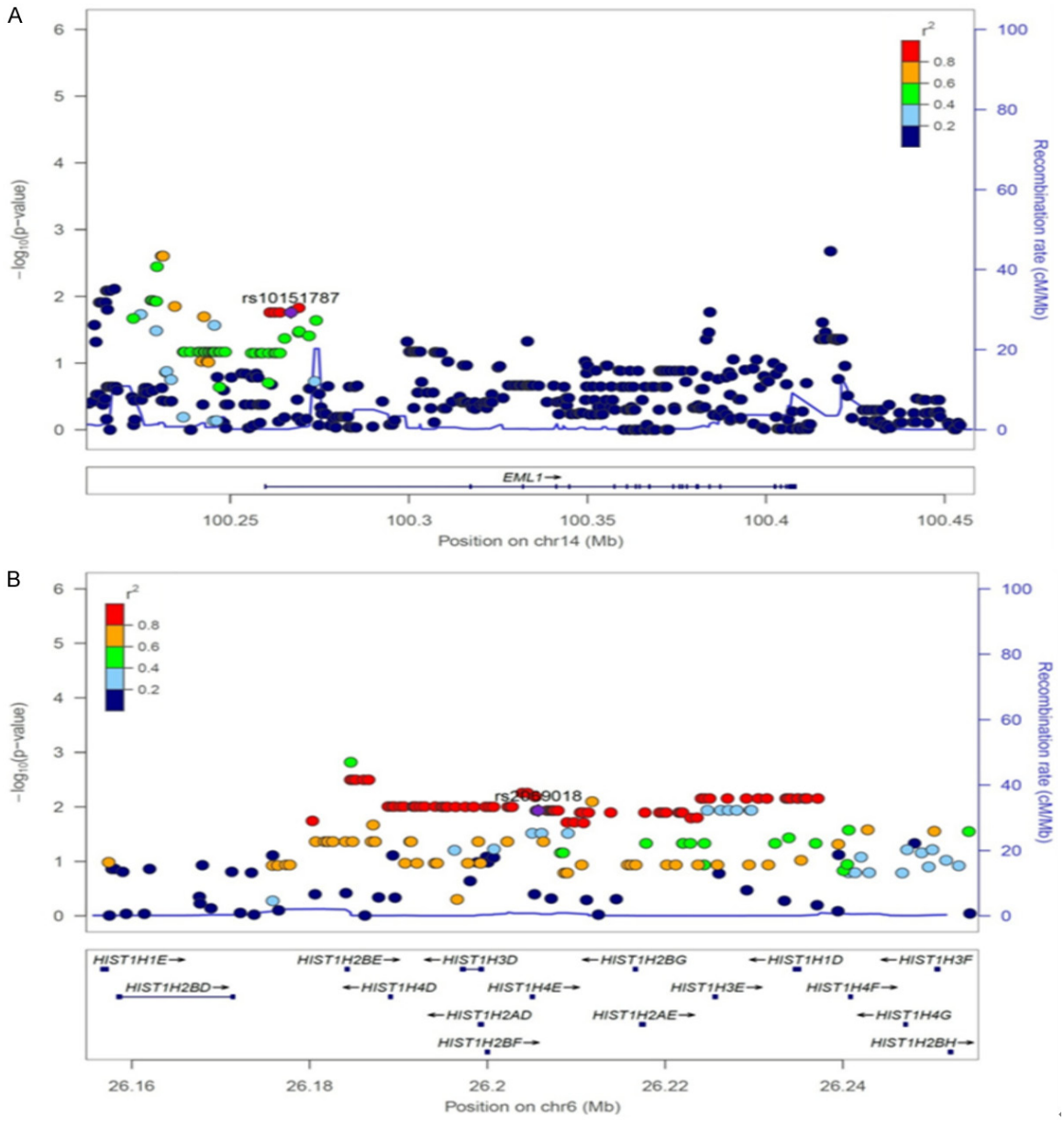
SNP	Chr	Position (hg38)	Gene	Haploreg v4.12[1]							
				LD (r^2)	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	GRASP QTL hits	Selected eQTL hits
rs1175649	1	112476655	*WNT2B*	1		ESC			4 altered motifs		6 hits
rs1175650	1	112476952	*WNT2B*	1					GR, ZID		8 hits
rs2798245	1	112464917	*WNT2B*	1		15 tissues	6 tissues		5 altered motifs		7 hits
rs11751812	6	26187334	*HIST1H4D*	1	ESC, IPSC	5 tissues			Smad3	12 hits	18 hits
rs11754140	6	26186976	*HIST1H4D*	1		4 tissues			10 altered motifs		10 hits
rs6906367	6	26187125	*HIST1H4D*	1	ESC	4 tissues	ESDR		5 altered motifs	13 hits	14 hits
rs11757394	6	26206694	*HIST1H4E*	1	22 tissues	5 tissues	26 tissues	5 bound proteins	DMRT4, Irf, LBP-9		8 hits
rs2069018	6	26205718	*HIST1H4E*	0.97	23 tissues		49 tissues	22 bound proteins	4 altered motifs	7 hits	14 hits
rs2069019	6	26205604	*HIST1H4E*	1	23 tissues		53 tissues	25 bound proteins	Nanog		8 hits
rs2069020	6	26205500	*HIST1H4E*	1	23 tissues		49 tissues	18 bound proteins	5 altered motifs		8 hits
rs56186759	6	26207181	*HIST1H4E*	1	14 tissues	12 tissues	MUS, OVRY	POL2, POL24H8	COMP1		8 hits
rs56220351	6	26206884	*HIST1H4E*	1	16 tissues	12 tissues			4 altered motifs		8 hits
rs16891407	6	26206299	*HIST1H4E*	1	23 tissues		53 tissues	15 bound proteins	STAT	7 hits	18 hits
rs77205516	6	26205128	HIST1H4E	1	23 tissues		27 tissues	4 bound proteins	Zfp105		8 hits
rs16891481	6	26242777	*HIST1H4F*	1	GI	5 tissues			Barhl1, Hoxa5	12 hits	17 hits
rs3734533	6	26240624	*HIST1H4F*	0.96	21 tissues	BRST	46 tissues	16 bound proteins	4 altered motifs	22 hits	15 hits
rs41521949	11	122597367	*UBASH3B*	1	BLD	11 tissues	6 tissues		4 altered motifs		1 hits
rs73018235	11	122599673	*UBASH3B*	1	BLD	9 tissues	KID, THYM		GR, LXR, STAT		1 hits
rs73018236	11	122600620	*UBASH3B*	1		BLD, HYM, SPLN			Pax-5, Zbtb3, Znf143		1 hits
rs7952454	11	122597548	*UBASH3B*	1	4 tissues	16 tissues	5 tissues		7 altered motifs		1 hits
rs61959910	13	50207885	*ARL11*	1		BLD, HRT, VAS		GATA2	4 altered motifs		
rs10151787	14	100266973	*EML1*	1					Crx, Pax-4		

Abbreviations: SNP, single-nucleotide polymorphism; Chr, chromosome; DNAse, deoxyribonuclease; QTL, quantitative trait loci; eQTL, expression quantitative trait loci; [1]Haploreg: https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php.


A
-log10(p)
HIST1H4E
rs2069018
EML1
rs10151787
BFDP=0.8
P=0.05
Chr1 Chr2 Chr3 Chr4 Chr5 Chr6 Chr7 Chr8 Chr9 Chr10 Chr11 Chr12 Chr13 Chr14 Chr15 Chr16 Chr17 Chr18 Chr19 Chr20 Chr21 Chr22



Supplementary Figure 1. Manhattan plot. A. Manhattan plot for 24,855 SNPs in the MDACC study. B. Manhattan plot for 1126 SNPs in the NHS/HPFS study. The blue horizontal line indicates *P* value equal to 0.05 and the red horizontal line represents BFDP value equal to 0.8. Abbreviations: SNP, single-nucleotide polymorphism; MDACC, The University of Texas MD Anderson Cancer Center; NHS/HPFS, Nurses' Health Study/Health Professionals Follow-up Study; BFDP, Bayesian false-discovery probability.

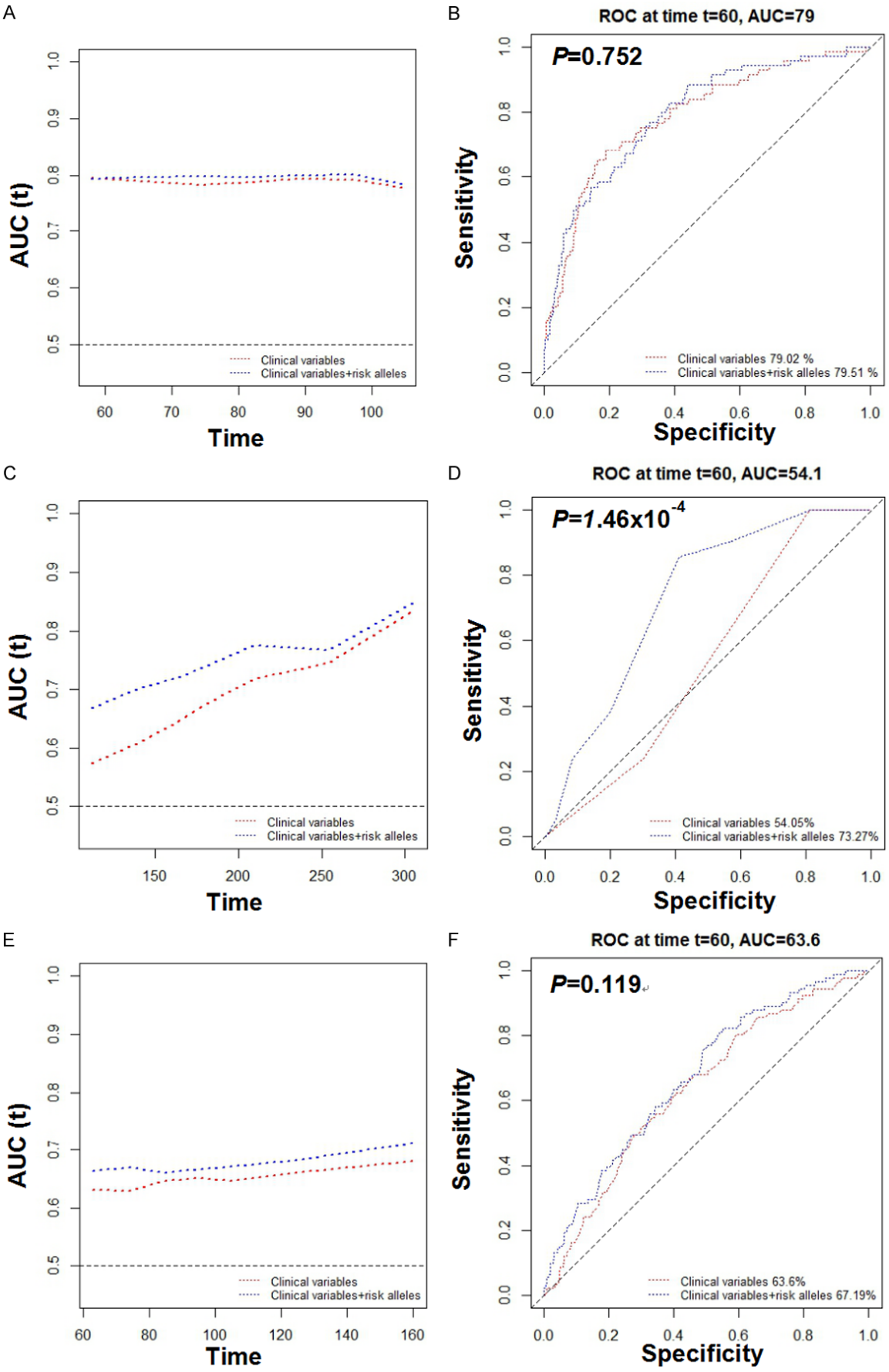


Supplementary Figure 2. Regional association plots for *EML1* rs10151787 and *HIST1H4E* rs2069018. Regional association plots contained 50 kb up and downstream of the gene regions in *EML1* (A) and *HIST1H4E* (B).

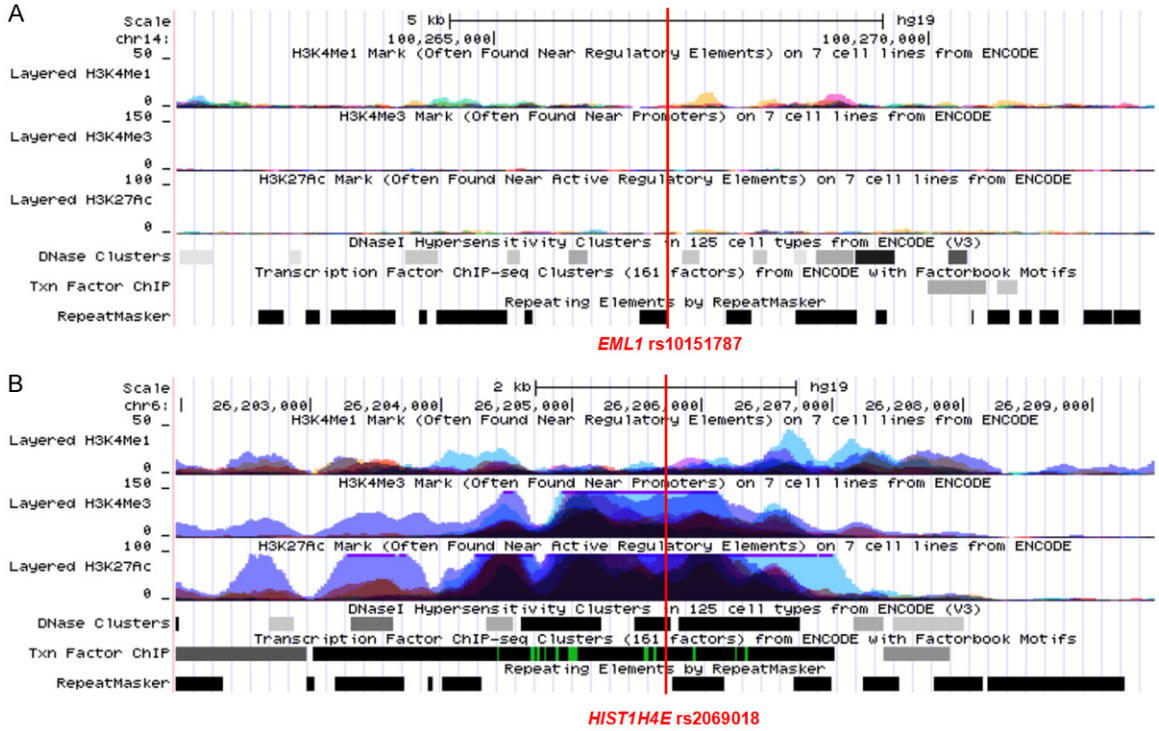
Supplementary Table 4. Stratified Cox analysis for risk alleles of the significant SNPs identified in the MDACC and NHS/HPFS genotyping datasets

Characteristics	0-1 risk allele[a]		2-4 risk alleles[a]		Univariate analysis		Multivariate analysis[b]		Interaction[c]
	All	Death (%)	All	Death (%)	HR (95% CI)	*P*	HR (95% CI)	*P*	
MDACC									
Age (years)									
≤ 50	321	22 (6.85)	50	9 (18.00)	2.68 (1.23-5.83)	0.013	2.62 (1.18-5.86)	0.019	
> 50	415	47 (11.33)	72	17 (23.61)	2.37 (1.36-4.13)	0.002	2.63 (1.47-4.72)	0.001	0.730
Sex									
Male	424	51 (12.03)	72	18 (25.00)	2.33 (1.36-3.99)	0.002	2.29 (1.32-4.00)	0.003	
Female	312	18 (5.77)	50	8 (16.00)	2.89 (1.26-6.66)	0.013	2.95 (1.24-7.00)	0.014	0.507
Stage									
I/II	615	35 (5.69)	94	16 (17.02)	3.22 (1.78-5.83)	<0.001	4.37 (2.36-8.08)	<.0001	
III/IV	121	34 (28.10)	28	10 (35.71)	1.41 (0.70-2.85)	0.343	1.27 (0.59-2.74)	0.537	0.297
Breslow thickness (mm)									
≤1	306	5 (1.63)	41	2 (4.88)	3.07 (0.60-15.83)	0.180	2.76 (0.06-9.05)	0.829	
>1	430	64 (14.88)	81	24 (29.63)	2.26 (1.42-3.62)	0.0006	2.54 (1.58-4.09)	0.0001	0.956
Ulceration									
No	585	36 (6.15)	96	12 (12.50)	2.10 (1.09-4.05)	0.026	1.91 (0.98-3.74)	0.058	
Yes	131	30 (22.90)	24	13 (54.17)	3.34 (1.74-6.42)	<0.001	3.23 (1.67-6.25)	0.0005	0.573
Missing	22								
Mitotic rate (mm^2)									
≤1	230	6 (2.61)	45	3 (6.67)	2.65 (0.66-10.61)	0.168	3.34 (0.56-19.43)	0.179	
>1	506	63 (12.45)	77	23 (29.87)	2.72 (1.69-4.39)	<.0001	2.50 (1.53-4.10)	0.0003	0.467
NHS/HPFS									
Age (years)									
≤ 50	61	2 (3.28)	11	1 (9.09)	2.78 (0.25-30.69)	0.403	2.87 (0.26-31.70)	0.391	
> 50	299	37 (12.37)	38	8 (21.05)	1.74 (0.81-3.73)	0.156	1.74 (0.81-3.73)	0.157	0.757
Sex									
Male	124	14 (11.29)	14	3 (21.43)	1.71 (0.49-5.96)	0.401	2.05 (0.57-7.41)	0.276	
Female	236	25 (10.59)	35	6 (17.14)	1.70 (0.70-4.13)	0.246	1.85 (0.76-4.52)	0.178	0.816

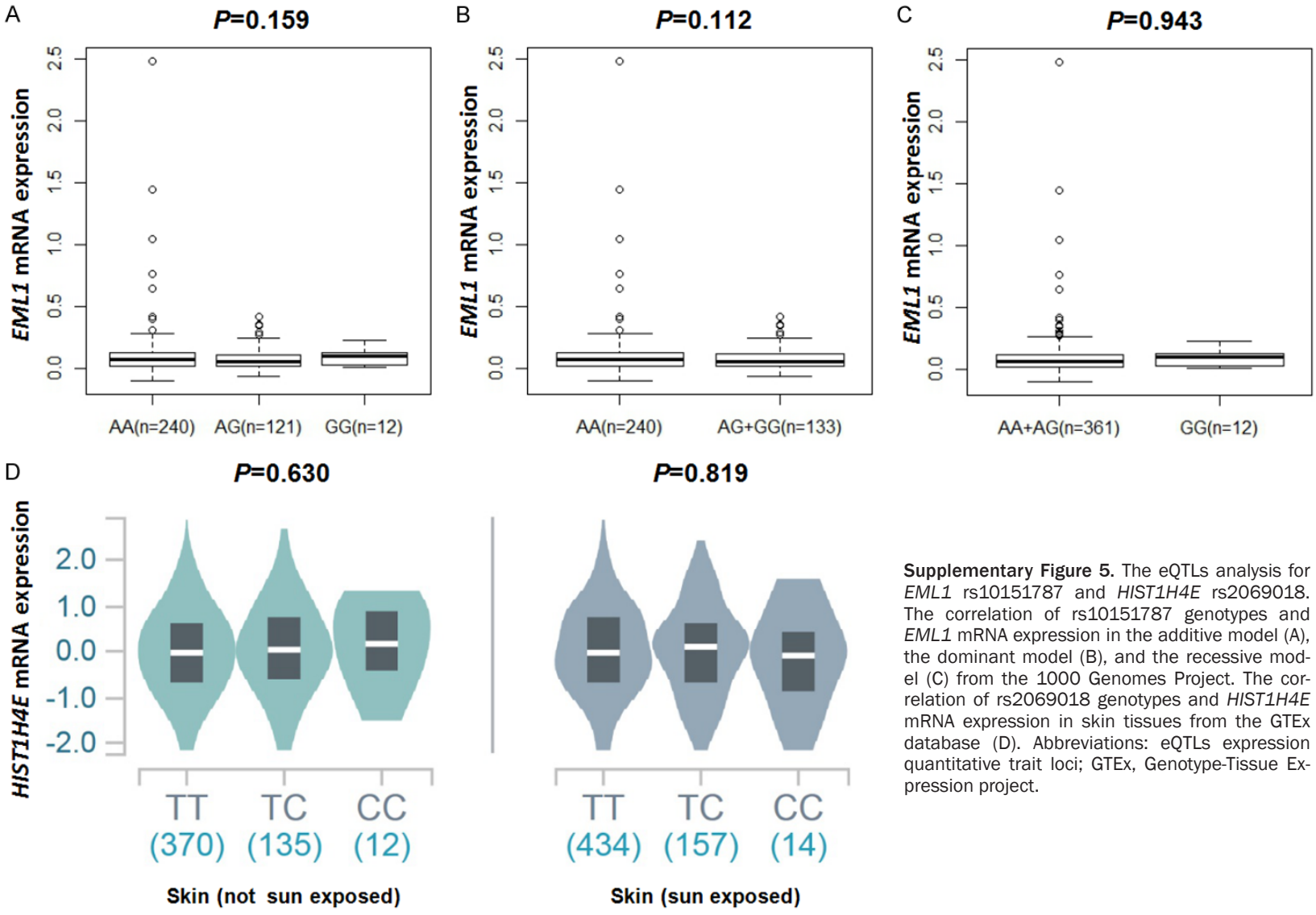
Abbreviations: SNP, single-nucleotide polymorphism; MDACC, The University of Texas MD Anderson Cancer Center; NHS, the Nurses' Health Study; HPFS, the Health Professionals Follow-up Study; HR, hazards ratio; CI, confidence interval. [a]Risk alleles include *EML1* rs10151787 G allele and *HIST1H4E* rs2069018 C allele; [b]Adjusted for age, sex, Breslow thickness, stage, ulceration and mitotic rate in Cox models of SNPs and CMSS in the MDACC dataset and adjusted for age and sex only in the NHS/HPFS datasets; [c]Interaction: the interaction between the risk alleles and each clinical variable.


A
AUC (t)
Time
Clinical variables
Clinical variables+risk alleles
B
ROC at time t=60, AUC=79
P=0.752
Sensitivity
Specificity
Clinical variables 79.02 %
Clinical variables+risk alleles 79.51 %
C
AUC (t)
Time
Clinical variables
Clinical variables+risk alleles
D
ROC at time t=60, AUC=54.1
P=1.46x10-4
Sensitivity
Specificity
Clinical variables 54.05%
Clinical variables+risk alleles 73.27%
E
AUC (t)
Time
Clinical variables
Clinical variables+risk alleles
F
ROC at time t=60, AUC=63.6
P=0.119
Sensitivity
Specificity
Clinical variables 63.6%
Clinical variables+risk alleles 67.19%

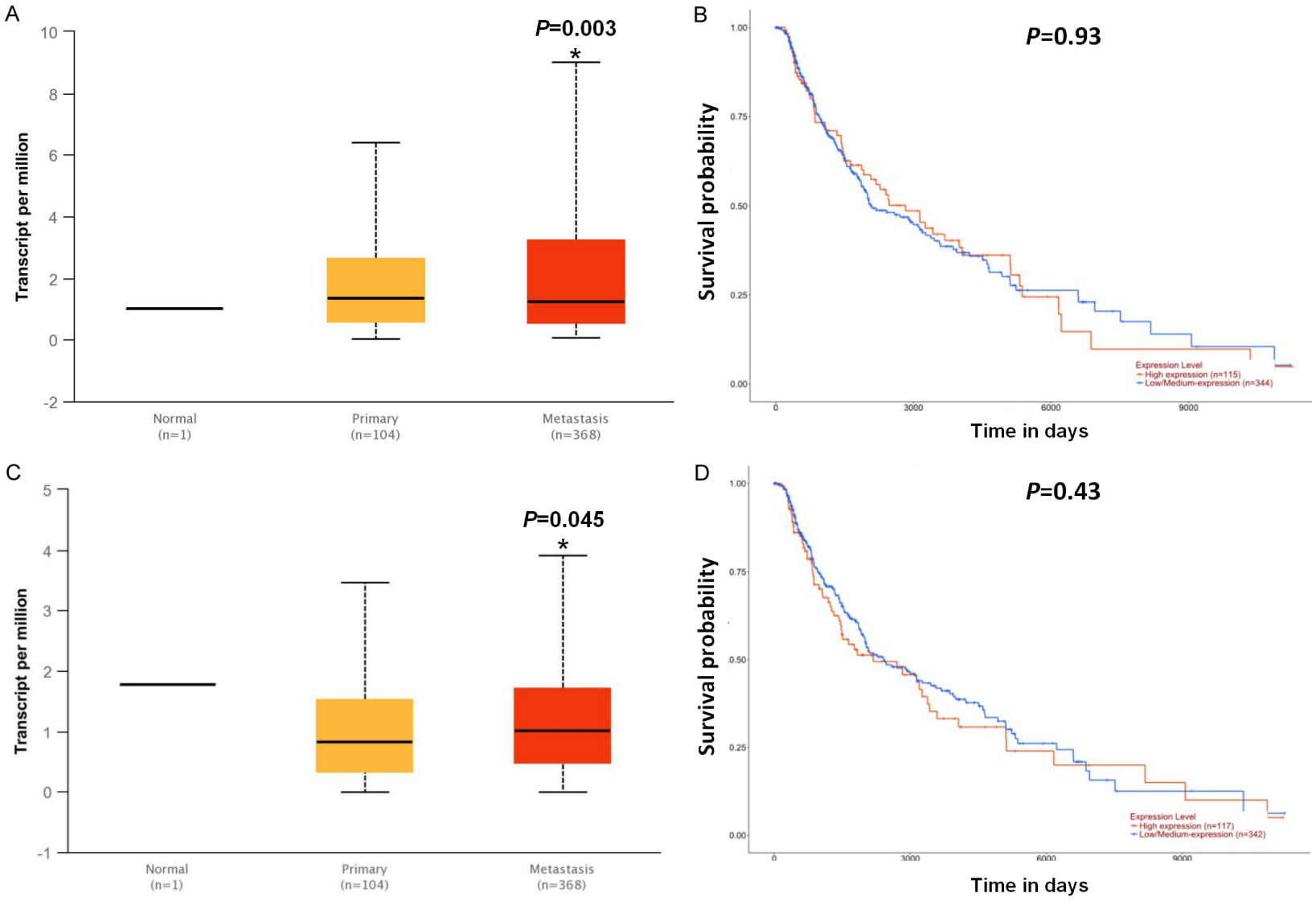
Supplementary Figure 3. ROC curve and time-dependent AUC estimation for five-year CMSS prediction in CM patients. The Time-dependent AUC estimation based on clinical variables plus risk alleles in the MDACC dataset (A), the NHS/HPFS dataset (C) and the combined MDACC and NHS/HPFS dataset (E). The five-year CMSS prediction by ROC curve in the MDACC dataset (B), the NHS/HPFS dataset (D) and the combined MDACC and NHS/HPFS dataset (F). Abbreviations: CMSS, cutaneous melanoma-specific survival; SNP, single-nucleotide polymorphism; AUC, area under receiver curve; MDACC, The University of Texas MD Anderson Cancer Center; NHS/HPFS, Nurses'Health Study/Health Professionals Follow-up Study; ROC, receiver operating characteristic.



Supplementary Figure 4. Functional prediction of EML rs10151787 and HIST1H4E rs2069018 in the ENCODE data. Location and functional prediction of *EML* rs10151787 (A). Location and functional prediction of *HIST1H4E* rs2069018 (B). The H3K27Ac, H3K4Me1, and H3K4Me3 tracks showed the genome-wide levels of enrichment of acetylation of lysine 27, the mono-methylation of lysine 4, and tri-methylation of lysine 4 of the H3 histone protein. DNase clusters track showed DNase hypersensitivity areas. Tnx factor track showed regions of transcription factor binding of DNA.



Supplementary Figure 5. The eQTLs analysis for *EML1* rs10151787 and *HIST1H4E* rs2069018. The correlation of rs10151787 genotypes and *EML1* mRNA expression in the additive model (A), the dominant model (B), and the recessive model (C) from the 1000 Genomes Project. The correlation of rs2069018 genotypes and *HIST1H4E* mRNA expression in skin tissues from the GTEx database (D). Abbreviations: eQTLs expression quantitative trait loci; GTEx, Genotype-Tissue Expression project.



Supplementary Figure 6. Differential mRNA expression analysis and survival prediction in the TCGA database. The difference of *EML1* (A) and *HIST1H4E* (C) mRNA expression between primary melanoma tissues and metastatic melanoma tissues in the TCGA database; *EML1* mRNA expression showed no significant correlation with melanoma survival probability in the TCGA database (B). *HIST1H4E* mRNA expression showed no significant correlation with melanoma survival probability in the TCGA database (D). Abbreviation: TCGA, The Cancer Genome Atlas.